MINISTRY OF HEALTH OF UKRAINE

ODESA NATIONAL MEDICAL UNIVERSITY

Department of Obstetrics and Gynecology

APPROVED

Vice-rector for scientific and pedagogical work

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METHODOLOGICAL RECOMMENDATIONS FOR LECTURES ON THE ACADEMIC DISCIPLINE "OBSTETRICS AND GYNECOLOGY"

for 5th year students

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Specialty: 222 "Medicine"

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LECTURE 1
"Physiology of pregnancy and childbirth. Methods of examination of pregnant women. Perinatal protection of the fetus"

RELEVANCE: During pregnancy there are progressive anatomical, physiological and biochemical changes not only confined to the genital organs but also to all systems of the body. This is principally a phenomenon of maternal adaptation to the increasing demands of the growing fetus. Unless well understood, these physiological adaptations of normal pregnancy can be misinterpreted as pathological.

Systematic supervision (examination and advice) of a woman during pregnancy is called antenatal (prenatal) care. The supervision should be regular and periodic in nature according to the need of the individual. Actually, prenatal care is the care in continuum that starts before pregnancy and ends at delivery and the postpartum period. Antenatal care comprises of careful history taking and examinations (general and obstetrical), advice given to the pregnant woman. Deep theoretical and practical knowledge of physiology of pregnancy and methods of obstetrical examination are needed for assessment of mother's health status, appropriate prenatal counseling and ensure successful obstetric outcome.

LEARNING OBJECTIVE is to gain basic knowledge about anatomical, physiological and biochemical changes during pregnancy, be familiar with the physiologic adaptations associated with a normal pregnancy, be able to differentiate between certain signs and symptoms that can be common to both disease processes and to physiologic adaptations of pregnancy, obtain knowledge about methods of obstetrical examination, appropriate prenatal counseling and supervision in order to provide successful obstetric outcome.

BASIC CONCEPTS: Fertilization and development of a fertilized egg. Placenta, its structure and function. Critical periods of embryo and fetal development. Influence of harmful factors on the embryo and fetus. Physiological changes in a woman's body during pregnancy. Hygiene and nutrition of a pregnant woman. Methods of examination of pregnant women: diagnosis of early and late pregnancy. Orientation of baby in the uterus. Management of physiological pregnancy. Laboratory diagnosis of HIV infection. Counseling in the context of HIV infection. The concept of counseling and its ethical principles. Counseling skills. Determination of maternity leave date and date of birth.

EDUCATIONAL MATERIALS

PHYSIOLOGICAL CHANGES DURING PREGNANCY

GENITAL TRACT CHANGES

Uterus

The effect of the hormonal stimulation is most marked upon the tissues of the genital tract, and the uterine muscle fibers grow to 15 times their prepregnancy length during pregnancy, whereas uterine weight increases from 50 g before

pregnancy to 1000 g at term. In the early weeks of pregnancy the growth is by hyperplasia, and more particularly by hypertrophy of the muscle fibers, with the result that the uterus becomes a thick-walled spherical organ. From the 20th week growth almost ceases and the uterus expands by distension, the stretching of the muscle fibers being due to the mechanical effect of the growing fetus. With distension the wall of the uterus becomes thinner and the shape cylindrical. The uterine blood vessels also undergo hypertrophy and become increasingly coiled in the first half of pregnancy, but no further growth occurs after this, and the additional length required to match the continuing uterine distension is obtained by uncoiling the vessels.

The uterus is derived from the two Müllerian ducts and the myometrium is made up of a thin external, largely longitudinal, layer; a thin inner, largely circular layer; and a thick, intricately interlaced middle layer, which comprises two spiral systems of interdigitating muscles derived from the two Müllerian ducts through which the blood vessels run. Apposition of two double curve muscle fibers give the figure of '8' form. Thus, when the muscles contract, they occlude the blood vessels running through the fibers and hence called living ligature. The proportion of muscle to connective tissue is greatest in the fundal area and diminishes as the lower segment of the uterus and cervix is approached, the lower half of the cervix having no more than 10% of muscle tissue.

The effect of the uterine distension is to stretch both interdigitating spiral systems and to increase the angle of crossing of the fibers, in the thinner lower segment area where the fibers cross at an angle of about 160° and are less stretched. Incision of the myometrium in this zone is anatomically more suitable, and experience of lower segment caesarean section confirms that healing is better.

Contractions (Braxton-Hicks): Uterine contraction in pregnancy has been named after Braxton-Hicks who first described its entity during pregnancy. From the very early weeks of pregnancy, the uterus undergoes spontaneous contraction. This can be felt during bimanual palpation in early weeks or during abdominal palpation when the uterus feels firmer at one moment and soft at another. Although spontaneous, the contractions may be excited by rubbing the uterus. The contractions are irregular, infrequent, spasmodic and painless without any effect on dilatation of the cervix. The patient is not conscious about the contractions. Intrauterine pressure remains below 8 mm Hg. Near term, the contractions become frequent with increase in intensity so as to produce some discomfort to the patient.

The lower uterine segment is that part of the lower uterus and upper cervix lying between the line of attachment of the peritoneum of the uterovesical pouch superiorly and the histological internal os inferiorly. It is that part of the uterus where the proportion of muscle diminishes, this muscle being replaced increasingly by connective tissue (75%), which forms 90% of the cervical tissues (mainly collagen fibers). Because of this the lower uterine segment becomes stretched in late pregnancy as the thickly muscled fundus draws it up from the relatively fixed cervix.

Cervix

The cervix becomes softer and swollen in pregnancy, with the result that the columnar epithelium lining the cervical canal becomes exposed to the vaginal secretions. This change in the cervix is due to oestradiol, which increases the hygroscopic properties of the cervical connective tissue and loosens the acid mucopolysaccharides (glycosaminoglycans) of the collagen-binding ground substance.

Prostaglandins act on the collagen fibers, especially in the last weeks of pregnancy. At the same time, collagenase is released from leucocytes, which also helps in breaking down collagen. The cervix becomes softer and more easily dilatable – the so-called ripening of the cervix. In this way the cervix is more easily able to dilate in labor.

Vagina

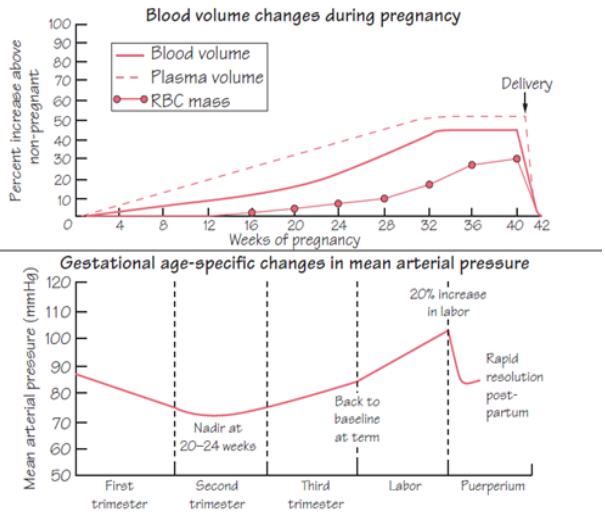
The vaginal mucosa becomes thicker, the vaginal muscle hypertrophies, and there is an alteration in the composition of the surrounding connective tissue, with the result that the vagina dilates more easily to accommodate the fetus during parturition. The changes, initiated by oestrogen, occur early in pregnancy and there is increased desquamation of the superficial vaginal mucosal cells with increased vaginal discharge in pregnancy. Should pathogens, whether bacterial, fungal (such as candida) or parasitic (such as trichomonas), enter the vagina they can more easily establish themselves and, consequently, vaginitis is more frequently found in pregnancy.

CARDIOVASCULAR SYSTEM

The plasma volume increases to fill the additional intravascular space created by the placenta and the blood vessels. The red cell mass increases to meet the increased demand for oxygen. Because the increase in the red cell mass is proportionately less than the increase in the plasma volume, the concentration of the erythrocytes in the blood falls, with a reduction in the haemoglobin concentration. Although the haemoglobin concentration falls to about 120 g/L at the 32nd week, a larger total haemoglobin is present than when not pregnant. Concurrently the number of white blood cells increases (to about 10 500/mL), as does the blood platelet count.

Central hemodynamic changes induced by pregnancy

Measurement	Non-pregnant	Term pregnant	Change
• Blood volume (mL)	3,500	5,000	+40%
• Mean arterial BP (mmHg)	86 ± 8	90 ± 6	no change
• Cardiac output (L/min)	4.3 ± 1	6.2 ± 1	+44%
• Heart rate (bpm)	71 ± 10	83 ± 10	+17%
• Central venous pressure (mmHg)	4 ±3	4 ± 3	no change
• Pulmonary capillary wedge pressure (mmHg)	6 ± 2	8 ± 2	no change
• Systemic vascular resistance (dyne/s per cm^{-5})	1,530 ± 520	1,210 ± 266	−21%
• Pulmonary vascular resistance (dyne/s per cm^{-5})	119 ± 47	78 ± 22	−35%
• Left ventricular stroke work index (g/m per m^2)	41 ± 8	48 ± 6	no change



Cardiovascular dynamics: To deal with the increased blood volume and the additional demand for oxygen in pregnancy the cardiac output increases by 30–50%. Most of the increased output is due to an increased stroke volume, but the heart rate increases by about 15%. The increased cardiac output is balanced by a decrease in the peripheral resistance. For these reasons, blood pressure falls in early pregnancy rising back to prepregnancy levels by the third trimester.

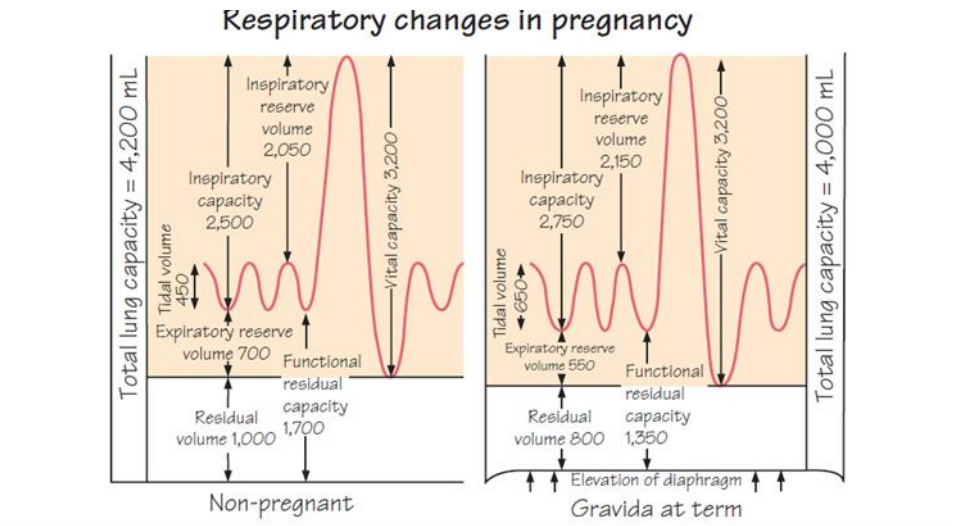
In common with other blood vessels, the veins of the legs become distended. The leg veins are affected particularly in late pregnancy because of the obstruction to venous return caused by the higher pressure of the venous blood returning from the uterus and the mechanical pressure of the uterus on the vena cava. This may lead to varicosities in the leg veins (and occasionally the vulvar veins) of susceptible women.

Regional distribution of the blood: The uterus receives the greatest proportion of the blood flow, which is vital to perfuse the placenta properly, reaching 500 mL/min by late pregnancy. Renal blood and plasma flow increase to 400 mL/min above non-pregnant levels by the 16th week of pregnancy, and remain at this high level to term. Blood flow through the capillaries of the skin and mucous membranes increases, reaching a maximum of 300–400 mL/min by the 36th week. The increased skin blood flow is associated with peripheral vasodilatation. This is the reason why pregnant women 'feel the heat', sweat easily and often profusely, and may complain of nasal congestion.

RESPIRATORY SYSTEM CHANGES

Respiratory adaptations during pregnancy are designed to optimize maternal and fetal oxygenation, and to facilitate transfer of CO2 waste from the fetus to the mother.

Many pregnant women report a subjective perception of shortness of breath (dyspnea) in the absence of pathology. The reason for this is unclear.



Effect of pregnancy on pulmonary-function testing

- Forced expiratory volume in one second (FEV_1)…no change in pregnancy (80–85% of vital capacity)
- Forced vital capacity (FVC)…..no change (~ 3.5 L)
- FEV_1/FVC ratio…..no change (>85%)
- Peak expiratory flow rate…..no change (~ 450 L/min)

The mechanics of respiration change with pregnancy. The ribs flare outward and the level of the diaphragm rises 4 cm.

During pregnancy, tidal volume increases by 200 mL (40%), resulting in a 100–200 mL (5%) increase in vital capacity and a 200 mL (20%) decrease in the residual volume, thereby leaving less air in the lungs at the end of expiration. The respiratory rate does not change. It is thought that this effect is due to the increased secretion of progesterone. The end-result is an increase in minute ventilation and a drop in arterial PCO_2 (see table below). Arterial PO_2 is slightly raises. A compensatory decrease in bicarbonate enables the pH to remain unchanged. Pregnancy thus represents a state of compensated respiratory alkalosis.

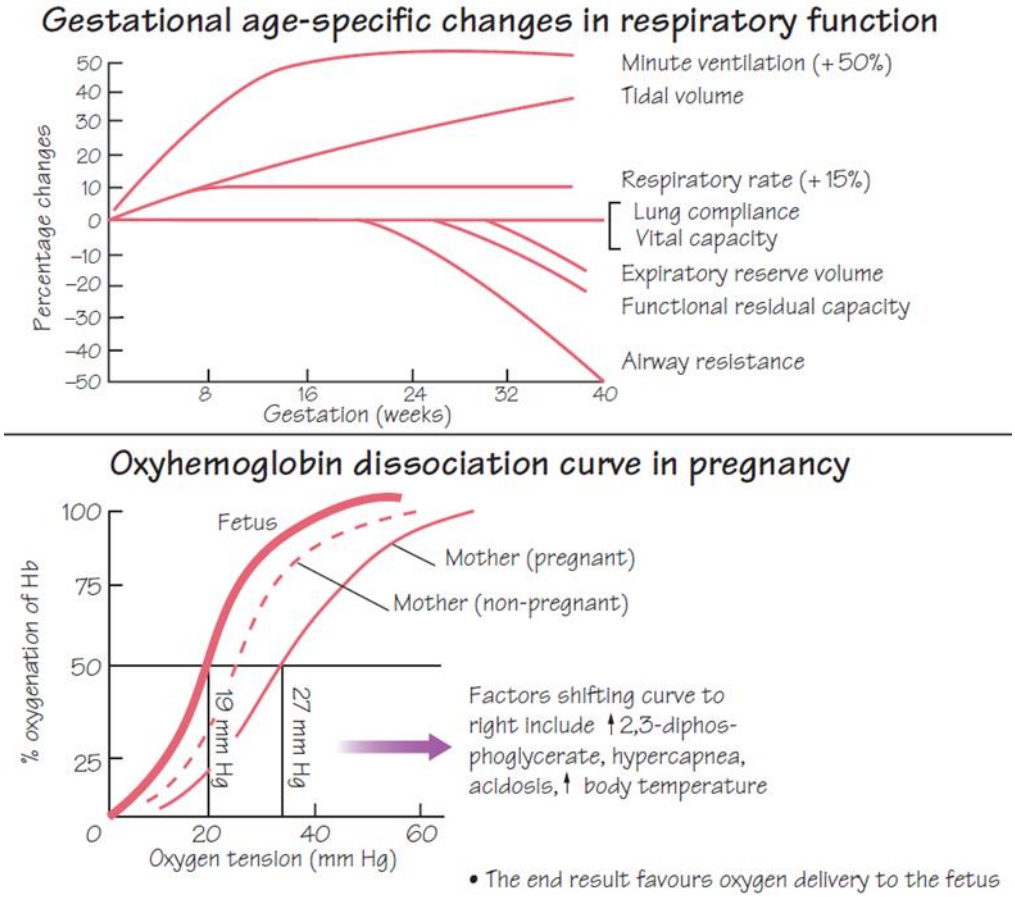
ALIMENTARY SYSTEM CHANGES

Nausea (“morning sickness”) occurs in >70% of pregnancies. Symptoms usually resolve by 17 weeks.

Progesterone causes relaxation of gastrointestinal smooth muscle, resulting in delayed gastric emptying and increased reflux.

Pregnancy predisposes to cholelithiasis (gallstones). Most gallstones in pregnancy are cholesterol stones.

Pregnancy is a “diabetogenic state” with evidence of insulin resistance and reduced peripheral uptake of glucose (due to increased levels of placental anti-insulin hormones, primarily human chorionic somatolactotropin or placental lactogen). These mechanisms are designed to ensure a continuous supply of glucose to the fetus.



RENAL SYSTEM CHANGES

Glomerular filtration rate (GFR) increases by 50% early in pregnancy, leading to an increase in creatinine clearance and a 25% decrease in serum creatinine and urea concentrations.

Increased GFR results in an increase in filtered sodium. Aldosterone levels increase two- to threefold to reabsorb this sodium.

Increased GFR also results in decreased resorption of glucose. As such, 15% of normal pregnant women exhibit glycosuria.

Mild hydronephrosis and hydroureter are common sonographic findings that are due to high progesterone levels and partial obstruction from the gravid uterus.

Five percent of pregnant women have bacteria in their urine. Pregnancy does not increase the incidence of asymptomatic bacteriuria, but such women are more likely to develop pyelonephritis (20–30%).

HEMATOLOGIC SYSTEM

Increased intravascular volume results in dilutional anemia. Elevated erythropoietin levels lead to a compensatory increase in total red cell mass, but never fully correct the anemia.

A modest increase in white blood cell count (leukocytosis) can be seen during pregnancy, but the differential count should not change.

Mild thrombocytopenia (<150,000 platelets/mL) is seen in 10% of pregnant women. This is probably dilutional and rarely clinically significant.

Pregnancy represents a hypercoagulable state with increased circulating levels of factors II (fibrinogen), VII, IX, and X. These changes protect the mother from excessive blood loss at delivery, but also predispose to thromboembolism.

IMMUNE SYSTEM CHANGES

Human chorionic gonadotrophin can reduce the immune response of pregnant women. In addition, serum levels of IgG, IgA and IgM decrease from the 10th week of pregnancy, reaching their lowest level at the 30th week and remaining at this level to term. These changes may account for the anecdotal increase in the risk of infection among pregnant women.

WEIGHT GAIN IN PREGNANCY

The better absorption of nutrients from the gut, the reduction of muscle tone and a reduction in thyroid activity produce a quiescence in the maternal metabolism. The body adapts to preserve and nourish the growing fetus. During pregnancy a woman inevitably gains weight. A healthy person may expect to gain 12.5 kg (range 9–15 kg) in pregnancy, of which 9 kg is gained in the last 20 weeks. The 'ideal' weight gain is only a guide, and an allowance should be made for individual variations. However, a woman whose prepregnancy weight is in the normal range (body mass index (BMI) 19–24.9) or who is overweight (BMI 25–29.9) should avoid excessive weight gain (more than 15 kg), as she may find it difficult to regain her prepregnancy weight after the birth. This is of concern to many women, who want to be reassured that they will regain their body shape and prepregnancy weight as soon as possible after the baby has been born.

After the birth there is a great variability in weight loss. Six weeks after the birth an average woman weighs 3 kg more than her prepregnancy weight. Six months after the birth she will weigh about 1kg more than she weighed before she became pregnant.

The situation is different for obese and underweight women, both during pregnancy and after birth. An obese woman (BMI >30) should be encouraged to limit her weight gain during pregnancy, as she has an increased risk that pre-eclampsia may occur and that she will have a large baby. She should have a glucose tolerance test performed to exclude gestational diabetes mellitus, and she should be advised to eat a sensible but not a very low-energy diet.

An underweight woman (BMI <18) should avoid becoming pregnant until she has gained weight, as she has a 20% chance of giving birth to a low-birthweight baby.

Weight gain in pregnancy is caused by several factors:

- The products of conception – the fetus, placenta and amniotic fluid
- The maternal factors – the uterus and breasts, the increased blood volume, the increased stores of fat, water retention.

Fetus, placenta and amniotic fluid: In the first 20 weeks of pregnancy fetal weight gain is slow; in the second 20 weeks it increases more rapidly. The weight gain of the placenta shows the reverse of that of the fetus. The amniotic fluid increases rapidly from the 10th week, being 300 mL at 20 weeks, 600 mL at 30

weeks, and peaking at 1000 mL at 35 weeks. After this a small decline in the total quantity of amniotic fluid occurs.

Maternal factors: The weight of the uterus increases throughout pregnancy. It is more rapid in the first 20 weeks, when myohyperplasia is occurring, than in the second 20 weeks when most of the enlargement is due to stretching of the muscle fibers. The breasts increase in weight throughout pregnancy owing to deposition of fat, increased retention of fluid, and growth of the glandular elements. The blood volume also increases throughout the pregnancy. The amount of fat deposited in adipose tissues depends on the amount of fat and carbohydrate in the diet. A gain of 2.5–3.0 kg of fat is usual, of which 90% is deposited in the first 30 weeks. The fat contains 90–105 MJ of energy, which can be released after birth for various activities, including breastfeeding. In a normal pregnancy the total body fluid increases by 6–8 L, of which 2–4 L is extracellular. Most of the fluid is retained before the 30th week, but a pregnant woman who has no clinical oedema retains 2–3 L of extracellular fluid in the last 10 weeks of pregnancy.

Energy

The resting metabolic rate (RMR) in pregnancy is 10–15% higher than in non-pregnant women. The extra energy required in the 40 weeks of pregnancy for the increased RMR, the growth of the fetus and placenta, the increase in size of the uterus and breasts, and the extra fat is about 250 MJ. This works out at about 0.9 MJ (about 215 kcal) a day – an amount provided by two slices of bread and 100 mL of milk. A pregnant woman does not need to eat for two!

ENDOCRINE GLANDS

The endocrine glands play very important role in the physiology of reproduction. At 6–8 weeks, there is transfer of functions of corpus luteum to the placenta — which acts temporarily as a new endocrine organ or powerhouse of hormone production.

Placenta produces a variety of hormones of which protein and steroid hormones are significantly important.

Human chorionic gonadotropin (hCG): hCG is a glycoprotein. Its molecular weight is 36000–40000 daltons. It consists of a hormone non-specific **a** (92 amino acids) and a hormone specific **b** (145 amino acids) subunit. hCG is chemically and functionally similar to pituitary luteinizing hormone. The a subunit is biochemically similar to LH, FSH and TSH whereas the b subunit is relatively unique to hCG. Placental GnRH may have a control on hCG formation.

Functions: (1) It acts as a stimulus for the secretion of progesterone by the corpus luteum of pregnancy. The rescue and maintenance of corpus luteum till 6 weeks of pregnancy is the major biological function of hCG.

(2) hCG stimulates Leydig cells of the male fetus to produce testosterone in conjunction with fetal pituitary gonadotropins. It is thus indirectly involved in the development of male external genitalia.

(3) It has got immunosuppressive activity which may inhibit the maternal processes of immunorejection of the fetus as a homograft.

(4) Stimulates both adrenal and placental steroidogenesis.

(5) Stimulates maternal thyroid because of its thyrotropic activity.

(6) Promotes secretion of relaxin from the corpus luteum.

Level of hCG at different periods of pregnancy: hCG is produced by the syncytiotrophoblast of the placenta and secreted into the blood of both mother and fetus. The plasma half life of hCG is about 36 hours. By radioimmunoassay, it can be detected in the maternal serum or urine as early as 8-9 days postfertilization. In the early pregnancy, the doubling time of hCG concentrations in plasma is 1.4–2 days. The blood and urine values reach maximum levels ranging 100 IU and 200 IU/mL between 60–70 days of pregnancy. The concentration falls slowly reaching a low level of 10–20 IU/ mL between 100–130 days. High levels of hCG could be detected in—(a) multiple pregnancy (b) hydatidiform mole or choriocarcinoma and relatively high in—(c) pregnancy with a 21-trisomy fetus (Down's syndrome). Plasma lower levels are found in ectopic pregnancies and in spontaneous abortion. hCG disappears from the circulation within 2 weeks following delivery.

Human placental lactogen (hPL): This is also known as human chorionic somatomammotropin (hCS). The hormone is synthesized by the syncytiotrophoblast of the placenta. The hormone is chemically and immunologically similar to pituitary growth hormone and prolactin. hPL in maternal serum is first detected during the 3rd week. The level rises progressively from 5 to 25 μg/mL until about 36 weeks. The plasma concentration of hPL is proportional to placental mass.

Functions: hPL antagonises insulin action. High level of maternal insulin helps protein synthesis. hPL causes maternal lipolysis and promotes transfer of glucose and amino acids to the fetus. As a potent angiogenic hormone, it helps to develop fetal vasculature. It promotes growth of breasts for lactation.

Pregnancy associated plasma protein—A (PAPP-A) is secreted by the syncytiotrophoblast. It acts as an immunosuppressant in pregnancy.

Estrogen: In late pregnancy, qualitatively, estriol is the most important amongst the three major estrogens. The site of its production is in the syncytiotrophoblast. The placenta is an incomplete endocrine organ as it has no capability of independent steroidogenesis like that of ovary. For steroidogenesis, it depends much on the precursors derived mainly from the fetal and partly from the maternal sources. Fetal adrenal gland and the placenta contain the complementary enzyme system.

Estriol is first detectable at 9 weeks (0.05 ng/mL) and increases gradually to about 30 ng/mL at term. Fetal death, fetal anomalies (adrenal atrophy, anencephaly, Down's syndrome), hydatidiform moles, placental sulfatase or aromatase deficiency are associated with low estriol.

Progesteron: Before 6 weeks of pregnancy, the corpus luteum secretes 17-ydroxyprogesterone. Following the development of trophoblast, progesterone is synthesized and secreted in increasing amount from the placenta. The daily production rate of progesterone in late normal pregnancy is about 250 mg. Low progesterone levels are observed in ectopic pregnancy and in abortion. High values are observed in hydatidiform mole, Rh-isoimmunization. After delivery, the plasma progesterone decreases rapidly and is not detectable after 24 hours.

Functions of the steroid hormones (estrogen and progesterone):

It is indeed difficult to single out the function of one from the other.

— Together they play an important role in the maintenance of pregnancy. Estrogen causes hypertrophy and hyperplasia of the uterine myometrium, thereby increasing the accommodation capacity and blood flow of the uterus. Progesterone in conjunction with estrogen stimulates growth of the uterus, causes decidual changes of the endometrium required for implantation and it inhibits myometrial contraction.

— Development and hypertrophy of the breasts during pregnancy are achieved by a number of hormones. Hypertrophy and proliferation of the ducts are due to estrogen, while those of lobulo-alveolar system are due to combined action of estrogen and progesterone (details — below).

— Both the steroids are required for the adaptation of the maternal organs to the constantly increasing demands of the growing fetus.

— Progesterone maintains uterine quiescence, by stabilizing lysosomal membranes and inhibiting prostaglandin synthesis. Progesterone and estrogens are antagonistic in the process of labor.

— Estrogens sensitizes the myometrum to oxytocin and prostaglandins. Estrogens ripen the cervix.

— Progesterone along with hCG and decidual cortisol inhibits T-lymphocyte mediated tissue rejection and protects the conceptus.

— Together they cause inhibition of cyclic fluctuating activity of gonadotropin–gonadal axis thereby preserving gonadal function.

Relaxin: It is a peptide hormone structurally related to insulin. The main source of production is the corpus luteum of the ovary but part of it may be also produced by the placenta and decidua. It has been claimed that relaxin relaxes myometrium, the symphysis and sacroiliac joints during pregnancy and also helps in cervical ripening by its biochemical effect.

DIAGNOSIS OF PREGNANCY

DURATION OF PREGNANCY: The duration of pregnancy has traditionally been calculated by the clinicians in terms of 10 lunar months or 9 calendar months and 7 days or 280 days or 40 weeks, calculated from the first day of the last menstrual period. This is called menstrual or gestational age. But, fertilization usually occurs 14 days prior to the expected missed period and in a previously normal cycle of 28 days duration, it is about 14 days after the first day of the period. Thus, the true gestation period is to be calculated by subtracting 14 days from 280 days, i.e. 266 days. This is called fertilization or ovulatory age and is widely used by the embryologist.

Symptoms of pregnancy can be divided into three groups: presumptive, probable and definitive.

— Presumptive symptoms and signs: It includes the features mainly appreciated by the women. (1) Amenorrhea (2) Frequency of micturition (3) Morning sickness (4) Fatigue (5) Breast changes (6) Skin changes (7) Quickening.

— Probable signs: (1) Abdominal enlargement (2) Braxton-Hicks contractions (3) External ballottement (4) Outlining the fetus (5) Changes in the size, shape and consistency of the uterus (6) Jacquemier's sign (7) Softening of the cervix (8) Osiander's sign (9) Internal ballottement (10) Immunological test.

— Definitive or absolute signs: (1) Palpation of fetal parts and perception of active fetal movements by the examiner at about 20th week (2) Auscultation of fetal heart sounds (3) Ultrasound evidence of embryo as early as 6th week and later on the fetus.

The following are the *presumptive symptoms and signs* (unrelated to uterus and fetus) of pregnancy:

Amenorrhea during the reproductive period in an otherwise healthy individual having previous normal periods, is likely due to pregnancy unless proved otherwise. However, cyclic bleeding may occur up to 12 weeks of pregnancy, until the decidual space is obliterated by the fusion of decidua vera with decidua capsularis. Such bleeding is usually scanty, lasting for a shorter duration than her usual and roughly corresponds with the date of the expected period. This is termed as placental sign. This type of bleeding should not be confused with the commonly met pathological bleeding, i.e. threatened abortion. Pregnancy, however, may occur in women who are previously amenorrheic — during lactation and puberty.

Fatigue is a frequent symptom which may occur early in pregnancy.

Morning sickness is inconsistently present in about 50% cases, more often in the first pregnancy than in the subsequent one. It usually appears soon following the missed period and rarely lasts beyond the first trimester. Its intensity varies from nausea on rising from the bed to loss of appetite or even vomiting. But it usually does not affect the health status of the mother.

Frequency of micturition is quite troublesome symptom during 8–12th week of pregnancy. It is due to (1) resting of the bulky uterus on the fundus of the bladder because of exaggerated anteverted position of the uterus, (2) congestion of the bladder mucosa and (3) change in maternal osmoregulation causing increased thirst and polyuria. As the uterus straightens up after 12th week, the symptom disappears.

Breast discomfort in the form of feeling of fullness and 'pricking sensation' is evident as early as 6–8th week specially in primigravidae.

The breast changes are evident between 6–8 weeks. There is enlargement with vascular engorgement evidenced by the delicate veins visible under the skin. The nipple and the areola (primary) become more pigmented specially in dark women. Secondary areola specially demarcated in primigravidae, usually appears at about 20th week. Montgomery's tubercles are prominent. Thick yellowish secretion (colostrum) can be expressed as early as 12th week. Variable degree of striae may be visible with advancing weeks.

Skeen changes: (1) Linear pigmented zone (linea nigra) extending from the symphysis pubis to ensiform cartilage may be visible as early as 20th week (2) Striae (both pink and white) of varying degree are visible in the lower abdomen, more towards the flanks (3) Chloasma: Pigmentation over the forehead and cheek may appear at about 24th week.

"Quickening" (feeling of life) denotes the perception of active fetal movements by the women. It is usually felt about the 20th week, about 2 weeks earlier in multiparae. Its appearance is a useful guide to calculate the expected date of delivery with reasonable accuracy.

The following are the *probable signs* (related to uterus and mum's feelings) of pregnancy:

Progressive enlargement of the lower abdomen by the growing uterus.

Pelvic changes — The pelvic changes are diverse and appear at different periods. Collectively, these may be informative in arriving at a diagnosis of pregnancy.

Jacquemier's or Chadwick's sign: It is the dusky hue of the vestibule and anterior vaginal wall visible at about 8th week of pregnancy. The discoloration is due to local vascular congestion.

Vaginal sign: (a) Apart from the bluish discoloration of the anterior vaginal wall (b) The walls become softened and (c) Copious non-irritating mucoid discharge appears at 6th week (d) There is increased pulsation, felt through the lateral fornices at 8th week called Osiander's sign.

Cervical signs: (a) Cervix becomes soft as early as 6th week (Goodell's sign), a little earlier in multiparae. The pregnant cervix feels like the lips of the mouth, while in the non-pregnant state, like that of tip of the nose. (b) On speculum examination, the bluish discoloration of the cervix is visible. It is due to increased vascularity.

Uterine signs: (a) Size, shape and consistency — The uterus is enlarged to the size of hen's egg at 6^{th} week, size of a goos' egg at 8th week and size of a fetal head by 12th week. The pyriform shape of the non-pregnant uterus becomes globular by 12 weeks.

(b)There may be asymmetrical enlargement of the uterus if there is lateral implantation. This is called Piskacek's sign where one half is firmer than the other half.

As pregnancy advances, symmetry is restored. The pregnant uterus feels soft and elastic.

(c) Hegar's sign: It is present in two-thirds of cases. It can be demonstrated between 6–10 weeks, a little earlier in multiparae. This sign is based on the fact that: (1) upper part of the body of the uterus is enlarged by the growing fetus (2) lower part of the body is empty and extremely soft and (3) the cervix is comparatively firm. Because of variation in consistency, on bimanual examination (two fingers in the anterior fornix and the abdominal fingers behind the uterus), the abdominal and vaginal fingers seem to oppose below the body of the uterus. Examination must be gentle to avoid the risk of abortion.

(d) Palmer's sign: Regular and rhythmic uterine contraction can be elicited during bimanual examination as early as 4–8 weeks. Palmer in 1949, first described it and it is a valuable sign when elicited. To elicit the test, the uterus is cupped between the internal fingers and the external fingers for about 2–3 minutes. During

contraction, the uterus becomes firm and well defined but during relaxation, becomes soft and ill defined. While the contraction phase lasts for about 30 seconds, with increasing duration of pregnancy, the relaxation phase increases. After 10th week, the relaxation phase is so much increased that the test is difficult to perform.

Fundal height is increased with progressive enlargement of the uterus. Approximate duration of pregnancy can be ascertained by noting the height of the uterus in relation to different levels in the abdomen.

The following formula is a useful guide for the purpose. Uterus remains a pelvic organ until 12th week, it may be just felt per abdomen as a suprapubic bulge. The height of the uterus is midway between the symphysis pubis and umbilicus at 16th week; at the level of umbilicus at 24th week and at the junction of the lower third and upper two-third of the distance between the umbilicus and ensiform cartilage at 28th week.

The distance between the umbilicus and the ensiform cartilage is divided into three equal parts. The fundal height corresponds to the junction of the upper and middle third at 32 weeks, up to the level of ensiform cartilage at 36th week and it comes down to 32 week level at 40th week because of engagement of the presenting part. To determine whether the height of the uterus corresponds to 32 weeks or 40 weeks, engagement of the head should be tested. If the head is floating, it is of 32 weeks pregnancy and if the head is engaged, it is of 40 weeks pregnancy.

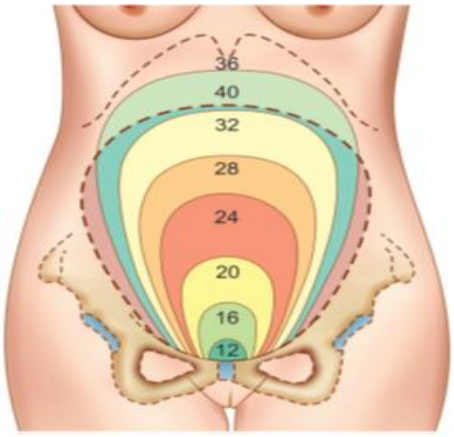
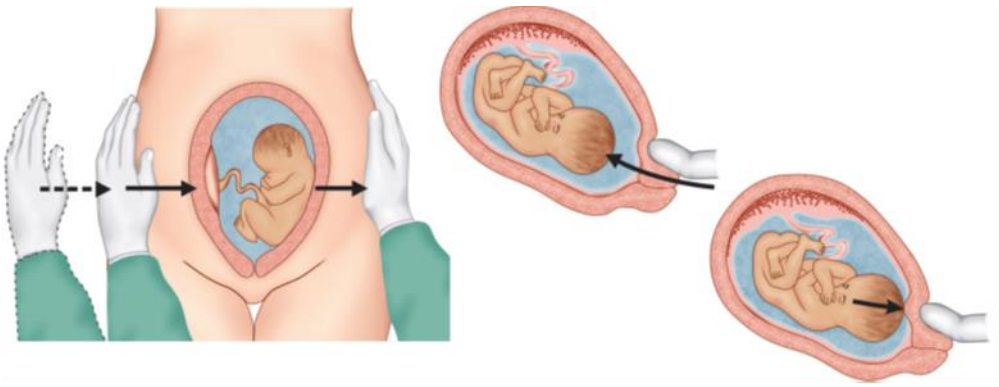


Fig.1: The level of fundus uteri at different weeks. Note the change of uterine shape

External ballottement is usually elicited as early as 20th week when the fetus is relatively smaller than the volume of the amniotic fluid. It is difficult to elicit in obese patients and in cases with scanty liquor amnii. It is best elicited in breech presentation with the head at the fundus.

Internal ballottement can be elicited between 16–28th week. The fetus is too small before 16th week and too large to displace after 28th week. However, the test may not be elicited in cases with scanty liquor amnii, or when the fetus is transversely placed.



A B C

Fig.2: (A) External ballottement; (B and C) Steps showing how to elicit internal ballottement

Immunological test: Principle: Pregnancy tests depend on detection of the antigen (hCG) present in the maternal urine or serum with antibody either polyclonal or monoclonal available commercially. Selection of time: Diagnosis of pregnancy by detecting hCG in maternal serum or urine can be made by 8 to 11 days after conception. The test is not reliable after 12 weeks.

Other uses of pregnancy tests: Apart from diagnosis of uterine pregnancy, the tests are employed in the diagnosis of ectopic pregnancy, to monitor pregnancy following in vitro fertilization and embryo transfer and to follow up cases of hydatidiform mole and choriocarcinoma. Test accuracy ranges from 98.6 – 99%. Non-pregnant level is below 1 mIU/mL.

Definitive or absolute signs are related to fetus.

Palpation of fetal parts and perception of active fetal movements by the examiner: Active fetal movements can be felt at intervals by placing the hand over the uterus as early as 20th week. It not only gives positive evidence of pregnancy but of a live fetus. The intensity varies from a faint flutter in early months to stronger movements in later months.

Auscultation: Fetal heart sound (FHS) is the most conclusive clinical sign of pregnancy. With an ordinary stethoscope, it can be detected between 18–20 weeks. The sounds resemble the tick of a watch under a pillow. Its location varies with the position of the fetus. The rate varies from 110–160 beats per minute.

Ultrasonography

Intradecidual gestational sac (GS) is identified as early as 29 to 35 days of gestation. Fetal viability and gestational age is determined by detecting the following structures by transvaginal ultrasonography. Gestational sac and yolk sac by 5 menstrual weeks; Fetal pole and cardiac activity — 6 weeks; Embryonic movements by 7 weeks. Fetal gestational age is best determined by measuring the CRL between 7 and 12 weeks (variation ± 5 days). Doppler effect of ultrasound can pick up the fetal heart rate reliably by 10th week.

Routine sonography at 18–20 weeks permits a detailed survey of fetal anatomy, placental localization and the integrity of the cervical canal. Gestational

age is determined by measuring the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). It is most accurate when done between 12 and 20 weeks (variation ± 8 days). BPD is measured at the level of the thalami and cavum septum pellucidum. BPD is measured from outer edge of the skull to the inner edge of the opposite side.

Fetal organ anatomy is surveyed to detect any malformation. Fetal viability is determined by real-time ultrasound. Absence of fetal cardiac motion confirms fetal death.

Gestational age estimation by BPD, HC, AC and FL in third trimester is less accurate (variation ± 3 weeks). Fetal AC at the level of the umbilical vein is used to assess gestational age and fetal growth profile (IUGR or macrosomia). Fetal weight estimation can be done using tables. Amniotic fluid volume assessment is done to detect oligohydramnios (AFI < 5) or polyhydramnios (AFI > 25). Placental anatomy: Location (fundus or previa), thickness (placentomegaly in diabetes) or other abnormalities are noted. Fetal life, number, presentation and organ anatomy as done in the first and second trimester are surveyed again.

Magnetic Resonance Imaging (MRI): MRI can be used for fetal anatomy survey, biometry and evaluation of complex malformations. Radiologic evidence of fetal skeletal shadow may be visible as early as 16th week.

CHRONOLOGICAL APPEARANCE OF SPECIFIC SYMPTOMS AND SIGNS OF PREGNANCY

AT 6–8 WEEKS: Symptoms — Amenorrhea, morning sickness, frequency of micturition, fatigue, breast discomfort. Signs: Breast enlargement, engorged veins visible under the skin; nipples and areola more pigmented. Internal examination reveals — positive Jacquemier's sign, softening of the cervix, bluish discoloration of the cervix and Osiander's sign; positive Hegar's and Palmer's sign. Uterine enlargement varies from hen's egg to medium size orange. Immunological tests will be positive. Sonographic evidence of gestational ring.

AT 16TH WEEK: Symptoms — Except amenorrhea, all the previous symptoms disappear. Signs: Breast changes — pigmentation of primary areola and prominence of Montgomery's tubercles, colostrum. Uterus midway between pubis and umbilicus, Braxton-Hicks contractions, uterine souffle, internal ballottement. Sonographic diagnosis.

AT 20TH WEEK: Symptoms — Amenorrhea, quickening (18th week). Signs: Appearance of secondary areola (20th week), linea nigra (20 weeks), uterus at the level of umbilicus at 24 weeks, Braxton-Hicks contractions, external ballottement (20th week), fetal parts (20 weeks), fetal movements (20 weeks), FHS (20 weeks), internal ballottement (16–28 weeks). Sonographic diagnosis.

SIGNS OF PREVIOUS CHILD BIRTH

The following are the features which are to be considered in arriving at a diagnosis of having a previous birth.

- ✓ Breasts become flabbier; nipples are prominent whoever breast-fed their infant; primary areolar pigmentation still remains and so also the white striae.
- ✓ Abdominal wall is laxer and looser. There may be presence of silvery white striae and linea alba.
- ✓ Uterine wall is less rigid and the contour of the uterus is broad and round, rather than ovoid.
- ✓ Perineum is lax and evidence of old scarring from previous perineal laceration or episiotomy may be found.
- ✓ Introitus is gaping and there is presence of carunculae myrtiformes.
- ✓ Vagina is roomier.
- ✓ Cervix: Nulliparous cervix is conical with a round external os. In parous women, it becomes cylindrical and the external os is a transverse patulous slit and may admit the tip of the finger. However, as a result of operative manipulation even a nulliparous cervix may be torn and resembles a multiparous cervix.

ESTIMATION OF GESTATIONAL AGE AND PREDICTION OF EXPECTED DATE OF DELIVERY

Gestational age is about 280 days calculated from the first day of the last normal menstrual period (LMP). Accurate LMP is the most reliable parameter for estimation of gestational age. But in significant number of cases (20–30%), the patients either fail to remember the LMP or report inaccurately. The matter becomes complicated when the conception occurs during lactation amenorrhea or soon following withdrawal of contraceptive pills (ovulation may be delayed for 4–6 weeks) or in cases with bleeding in early part of pregnancy. The following parameters either singly or in combination are useful in predicting the gestational age with fair degree of accuracy.

PATIENT'S STATEMENT

— Date of fruitful coitus: If the patient can remember the date of the single fruitful coitus with certainty, it is quite reliable to predict the expected date of delivery with accuracy of 50% within 7 days on either side. 266 days are to be added to the date of the single fruitful coitus to calculate the expected date.

— Naegele's formula: Provided the periods are regular, it is very useful and commonly practiced means to calculate the expected date. Its prediction range is about 50% with 7 days on either side of EDD. If the interval of cycles is longer, the extra days are to be added and if the interval is shorter, the lesser days are to be subtracted to get the EDD.

Calculation of the expected date of delivery (EDD)

This is done according to Naegele's formula (1812) by adding 9 calendar months and 7 days to the first day of the last normal (28 day cycle) period. Alternatively, one can count back 3 calendar months from the first day of the last period and then add 7 days to get the expected date of delivery; the former method is commonly employed.

Example: The patient had her first day of last menstrual period on 1st January. By adding 9 calendar months it comes to 1st October and then add 7 days, i.e. 8th October, which becomes the expected date of delivery. For IVF pregnancy date of LMP is 14 days prior to date of embryo transfers (266 days).

— Date of quickening: A rough idea about the probable date of delivery can be deduced by adding 20 weeks in primigravidae and 22 weeks in multiparae to the date of quickening.

PREVIOUS RECORDS: The required weeks are to be added to make it 40 weeks.

— Size of the uterus prior to 12 weeks more precisely corresponds with the period of amenorrhea.

— Height of the uterus above the symphysis pubis in relation to the landmarks on the abdominal wall.

— Auscultation of FHR at the earliest by 18–20 weeks using ordinary stethoscope and that using Doppler principle at 10th week. Palpation of fetal parts at the earliest by 20th week.

— Recording of positive pregnancy test using immunological principle at first missed period by earliest.

— Ultrasonographic findings at the earliest are: (a) Gestation sac — at 5 weeks. (b) Measurement of crown rump length (CRL) detected at 7 weeks, approximates 10 mm; at 10 weeks – 34 mm (CRL in cm + 6.5 = weeks of pregnancy). Crown — Rump Length (CRL) is most accurate. (Variation ± 5 days). Second trimester by BPD, HC, AC and FL measurement. Most accurate when done between 12 and 20 weeks (variation ± 8 days). Third trimester — Less reliable, variation ± 16 days.

— Lightening: Following the appearance of the features suggestive of lightening, the labor is likely to commence within 3 weeks.

ESTIMATION OF FETAL WEIGHT

- Height of the uterus above the symphysis pubis in centimeters multiplied by abdomen circumference measured on the level of umbilicus in either case gives the weight of the fetus in grams. Example — Height of the uterus above the symphysis pubis = 34 cm and the abdomen circumference = 95 cm. The weight of the fetus will be 34 × 95 = 3230 g. However, the approximate size of the fetus is modified by the amount of liquor amnii and thickness of the abdominal wall.
- Sonography: Fetal weight has been estimated by combining a number of biometric data, e.g. BPD, HC, AC and FL. Tables (Hadlock, Shepard) are currently in use (computer software). Estimated fetal weight likely to be within 10 percent of actual weight.

THE FETUS-IN-UTERO

The fetus lies inside the uterus in a closed sac filled with liquor amnii. It has enough freedom of movement until the later months of pregnancy, when it becomes

relatively fixed. Till then, periodic examination is essential to note its lie, presentation, position and attitude. Incidental idea can be gained about the size of the fetus or amount of liquor amnii.

LIE: The lie refers to the relationship of the long axis of the fetus to the long axis of the centralized uterus or maternal spine, the commonest lie being longitudinal (99.5%). The lie may be transverse or oblique; sometimes the lie is unstable until labor sets in, when it becomes either longitudinal or transverse.

PRESENTATION: The part of the fetus which occupies the lower pole of the uterus (pelvic brim) is called the presentation of the fetus. Accordingly, the presentation may be cephalic (96.5%), podalic (3%) or shoulder and other (0.5%). When more than one part of the fetus present, it is called compound presentation PRESENTING PART: The presenting part is defined as the part of the presentation which overlies the internal os and is felt by the examining finger through the cervical opening. Thus, in cephalic presentation, the presenting part may be vertex (commonest), brow or face, depending upon the degree of flexion of the head.

Similarly, the fetal legs in a breech presentation may be flexed (complete breech), extended (frank breech) or a foot may be present (footling). However, the term presentation and presenting part are often used synonymously and expressed more commonly in clinical practice according to the latter definition.

ATTITUDE: The relation of the different parts of the fetus to one another is called attitude of the fetus. The universal attitude is that of flexion. During the later months, the head, trunk and limbs of the fetus maintain the attitude of flexion on all joints and form an ovoid mass that corresponds approximately to the shape of uterine ovoid. The characteristic flexed attitude may be modified by the amount of liquor amnii. There may be exceptions to this universal attitude and extension of the head may occur (deflexed vertex, brow or face presentation, according to the degree of extension), or the legs may become extended in breech. The course of labor in such circumstances may be modified accordingly.

DENOMINATOR: It is an arbitrary bony fixed point on the presenting part which comes in relation with the various quadrants of the maternal pelvis. The following are the denominators of the different presentations—occiput in vertex, mentum (chin) in face, frontal eminence in brow, sacrum in breech and acromion in shoulder.

POSITION: It is the relation of the denominator to the different quadrants of the pelvis. For descriptive purpose, the pelvis is divided into equal segments of 45° to place the denominator in each segment. Thus, theoretically, there are 8 positions with each presenting part.

Anterior, posterior, right or left position is referred in relation to the maternal pelvis, with the mother in erect position. However, some have retained the conventional description of four vertex positions. Vertex occupying the left anterior quadrant of the pelvis is the commonest one and is called left occipitoanterior (LOA). This is the first vertex position. Similarly, right occipitoanterior (ROA) is the second vertex; right occipitoposterior (ROP) third vertex and left occipitoposterior (LOP) is the fourth vertex position.

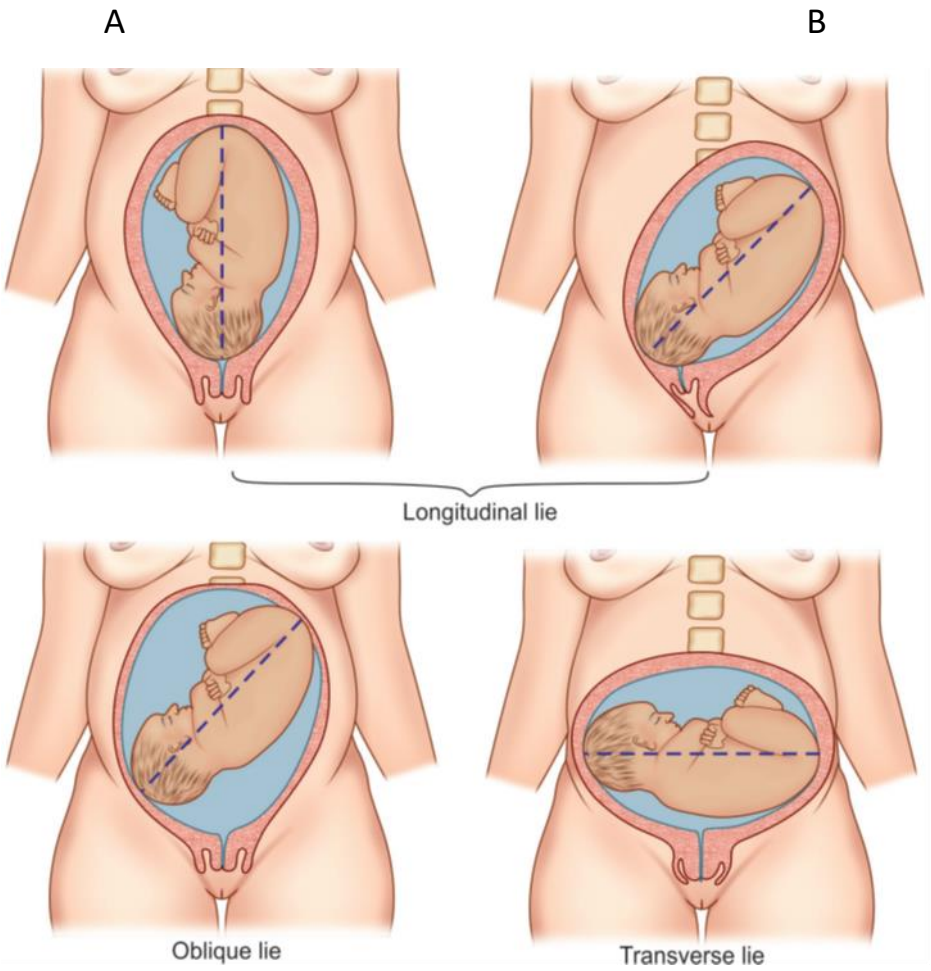


Fig. 3: Fetal lie. (B), the fetus seems to lie in oblique position in relation to the maternal spine but remains in longitudinal lie in relation to uterine axis. Correction of the uterine obliquity rectifies apparent oblique lie of the fetus (A)

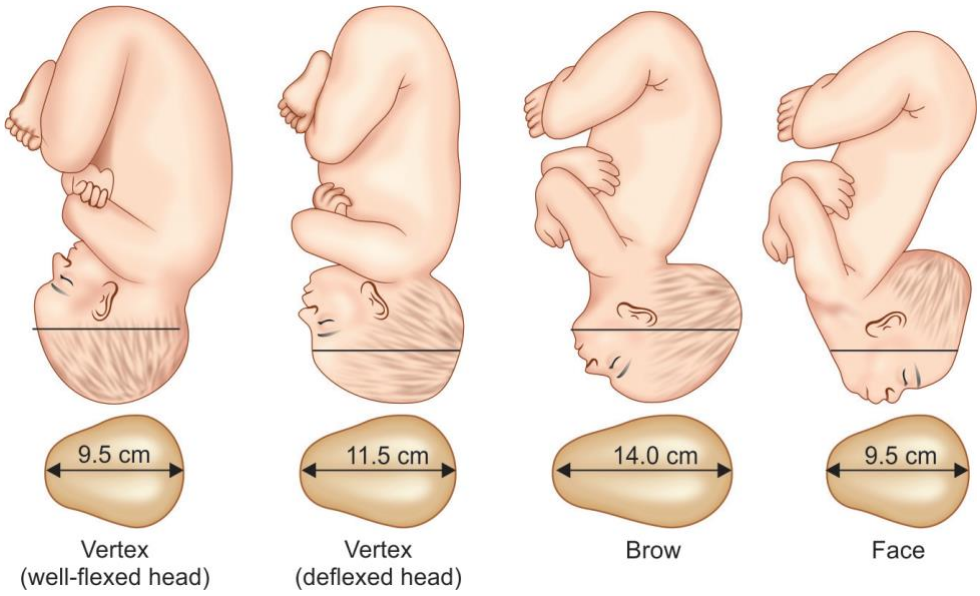


Fig. 4: Varieties of cephalic presentations in different attitude

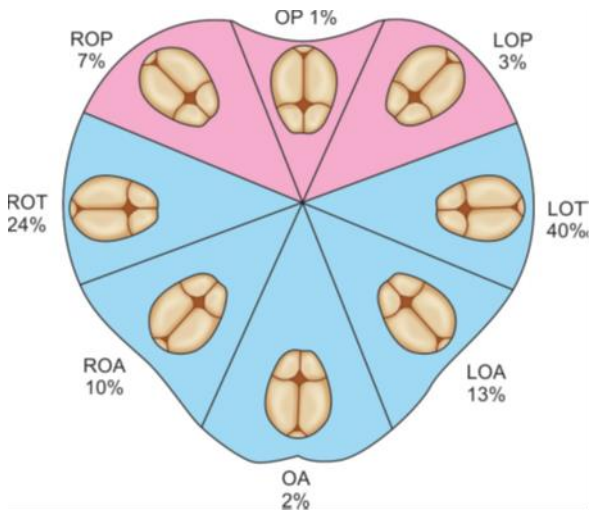


Fig.5: The position and relative frequency of the vertex at the onset of labor

The fetus in the attitude of flexion assumes a shape of an ovoid with its long vertico-podalic axis measuring about 25 cm at term. The fetus accommodates comfortably along the long axis of the ovoid shape of the uterine cavity at term. Hence, there is preponderance of longitudinal lie.

The cephalic presentation, being the absolute majority amongst the longitudinal lie, can be explained by: (1) Gravitation—the head being heavier comes down to the bottom. (2) Adaptation — the smallest circumference of the flexed head is about 27.5 cm and the circumference of the breech with both thighs flexed is about 32.5 cm. Thus the cephalic and the podalic poles can be comfortably accommodated in the narrow lower pole and the wider fundal area of the uterus respectively.

METHODS OF OBSTETRICAL EXAMINATION

ABDOMINAL EXAMINATION: A thorough and systemic abdominal examination beyond 28 weeks of pregnancy can reasonably diagnose the lie, presentation, position and the attitude of the fetus. It is not unlikely that the lie and presentation of the fetus might change, specially in association with excess liquor amnii and hence periodic checkup is essential.

Abdominal examination

Preliminaries: Verbal consent for examination is taken. The patient is asked to evacuate the bladder. She is then made to lie in dorsal position with the thighs slightly flexed. Abdomen is fully exposed. The examiner stands on the right side of the patient.

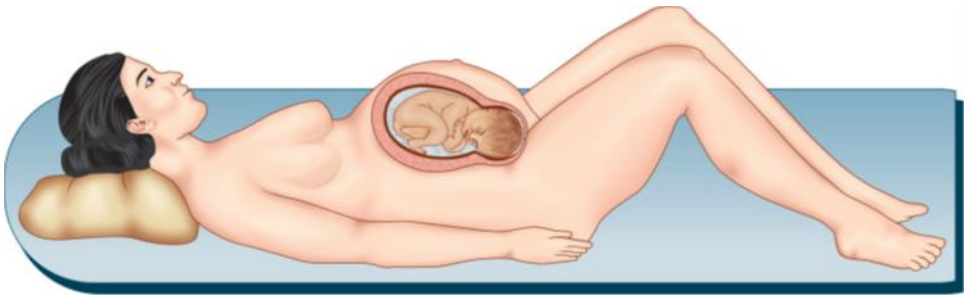


Fig.6: Position of the woman during obstetric examination

Inspection: To note (1) whether the uterine ovoid is longitudinal or transverse or oblique (2) contour of the uterus—fundal notching, convex or flattened anterior wall, cylindrical or spherical shape (3) undue enlargement of the uterus (4) skin condition of abdomen for evidence of ringworm or scabies and (5) any incisional scar mark on the abdomen.

Palpation: *Symphysis fundal height (SFH)*: The uterus is to be centralized if it is deviated. The upper border of the fundus is located by the ulnar border of the left hand and this point is marked. The distance between the upper border of the symphysis pubis upto the marked point is measured by a tape in centimeter. After 24 weeks, the SFH measured in cm corresponds to the number of weeks up to 36 weeks. A variation of ± 2 cm is accepted as normal.

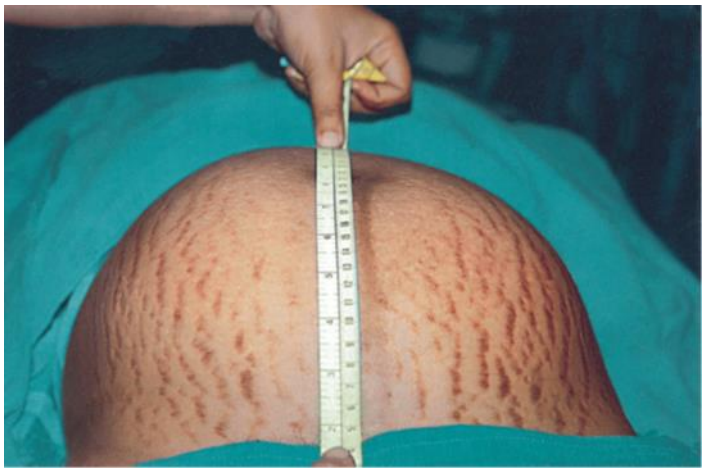


Fig. 7: Symphysis fundal height (SFH)

There are conditions where the height of the uterus may not correspond with the period of amenorrhea. The conditions where the height of the uterus is more than the period of amenorrhea are: (1) mistaken date of the last menstrual period (2) twins (3) polyhydramnios (4) big baby (5) pelvic tumors— ovarian or fibroid (6) hydatidiform mole and (7) concealed accidental hemorrhage. The condition where the height of the uterus is less than the period of amenorrhea are: (1) mistaken date

of the last menstrual period (2) scanty liquor amnii (3) fetal growth retardation and (4) intrauterine fetal death.

Obstetric grips (Leopold maneuvers)

Palpation should be conducted with utmost gentleness. Clumsy and purposeless palpation is not only uniformative but may cause undue uterine irritability. During Braxton-Hicks contraction or uterine contraction in labor, palpation should be suspended.

Fundal grip (First Leopold): The palpation is done facing the patient's face. The whole of the fundal area is palpated using both hands laid flat on it to find out which pole of the fetus is lying in the fundus: (a) broad, soft and irregular mass suggestive of breech, or (b) smooth, hard and globular mass suggestive of head. In transverse lie, neither of the fetal poles are palpated in the fundal area.

Lateral or umbilical grip (Second Leopold): The palpation is done facing the patient's face. The hands are to be placed flat on either side of the umbilicus to palpate one after the other, the sides and front of the uterus to find out the position of the back, limbs and the anterior shoulder. The back is suggested by smooth curved and resistant feel. The 'limb side' is comparatively empty and there are small knob like irregular parts. After the identification of the back, it is essential to note its position whether placed anteriorly or towards the flank or placed transversely. Similarly, the disposition of the small parts, whether placed to one side or placed anteriorly occupying both the sides, is to be noted. The position of the anterior shoulder is to be sought for. It forms a well marked prominence in the lower part of the uterus above the head. It may be placed near the midline or well away from the midline.

Pawlik's grip (Third Leopold): The examination is done facing towards the patient's face. The overstretched thumb and four fingers of the right hand are placed over the lower pole of the uterus keepingthe ulnar border of the palm on the upper border of the symphysis pubis. When the fingers and the thumb are approximated, the presenting part is grasped distinctly (if not engaged) and also the mobility from side to side is tested. In transverse lie, Pawlik's grip is empty.

Pelvic grip (Fourth Leopold): The examination is done facing the patient's feet. Four fingers of both the hands are placed on either side of the midline in the lower pole of the uterus and parallel to the inguinal ligament. The fingers are pressed downwards and backwards in a manner of approximation of finger tips to palpate the part occupying the lower pole of the uterus (presentation). If it is head, the characteristics to note are: (1) precise presenting area (2) attitude and (3) engagement.

To ascertain the presenting part, the greater mass of the head (cephalic prominence) is carefully palpated and its relation to the limbs and back is noted. The

attitude of the head is inferred by noting the relative position of the sincipital and occipital poles. The engagement is ascertained noting the presence or absence of the sincipital and occipital poles or whether there is convergence or divergence of the finger tips during palpation. This pelvic grip using both the hands is favored as it is most comfortable for the woman and gives most information.

Auscultation

Auscultation of distinct fetal heart sounds (FHS) not only helps in the diagnosis of a live baby but its location of maximum intensity can resolve doubt about the presentation of the fetus. The fetal heart sounds are best audible through the back (left scapular region) in vertex and breech presentation where the convex portion of the back is in contact with the uterine wall. However, in face presentation, the heart sounds are heard through the fetal chest.

As a rule, the maximum intensity of the FHS is below the umbilicus in cephalic presentation and around the umbilicus in breech. In different positions of the vertex, the location of the FHS depends on the position of the back and the degree of descent of the head. In occipitoanterior position, the FHS is located in the middle of the spinoumbilical line of the same side. In occipitolateral position, it is heard more laterally and in occipitoposterior position, well back towards the mother's flank on the same side.

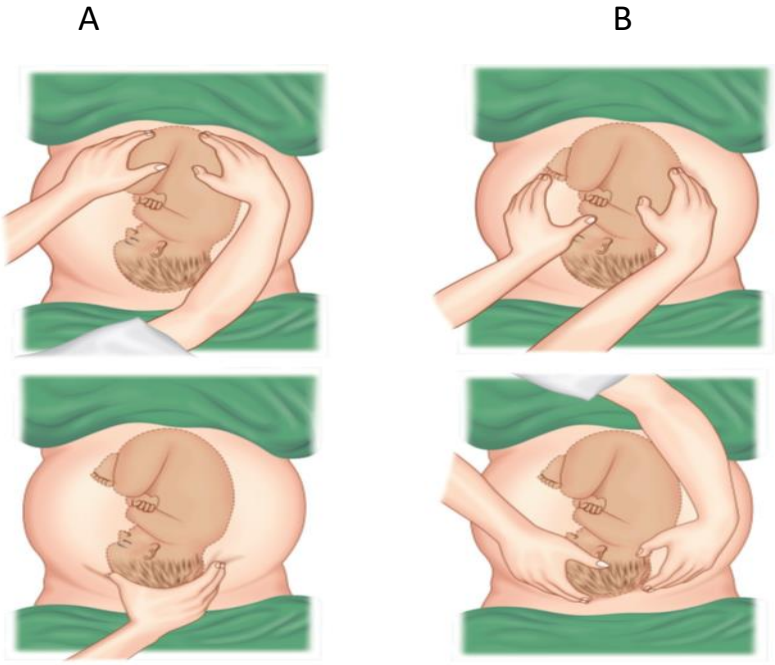


Fig.8: Obstetric grips (Leopold maneuvers): (A) Fundal grip (first Leopold); (B) Lateral grip (second Leopold); (C) Pawlik's grip (third Leopold); (D) Pelvic grip (fourth Leopold)

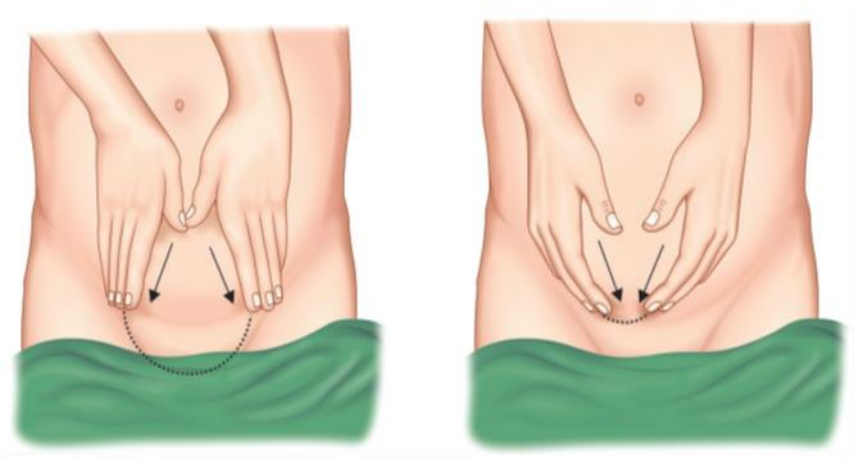
INTERNAL EXAMINATION: The diagnosis of the presentation and position of the fetus may not be accurate by internal examination during pregnancy when the cervix remains closed. However, during labor, accurate information may be obtained by palpation of the sagittal suture and fontanelles through the open cervix. Stress for strict aseptic precautions during vaginal examination needs no emphasis.

ULTRASONOGRAPHY: The diagnosis of the lie, presentation and position may be difficult in the presence of marked obesity, irritable uterus, excessive liquor amnii and deeply engaged head, specially in primigravidae. Ultrasonography can locate the head and the body.

ENGAGEMENT

When the greatest horizontal plane, the biparietal, has passed the plane of the pelvic brim, the head is said to be engaged.

Diagnosis: First pelvic grip: (1) Both the poles (sinciput and occiput) are not felt per abdomen. However, the sincipital pole can be felt with difficulty even though the head is engaged (2) Divergence of the examining fingers of both the hands while trying to push downwards on the lower abdomen. Convergence of the fingers while palpating the lateral aspects of the fetal head indicates that the head is not yet engaged.



A B

Fig.9: Abdominal palpation to determine engagement of the head: (A) Divergence of fingers—engaged head, (B) Convergence fingers—not engaged

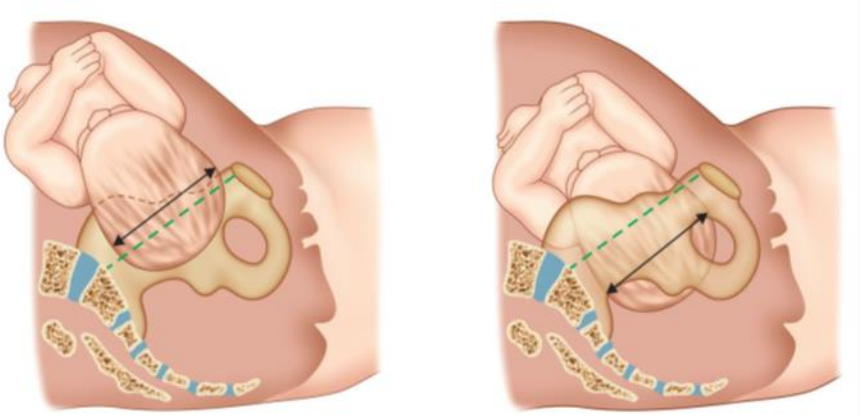


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Fig. 10: The relationship of the biparietal diameter to the pelvic brim and that of lower pole of the head to the ischial spines in: (A) Non-engaged head; (B) Engaged head

Vaginal Examination: Lower pole of the unmoulded head is usually at or below the level of the ischial spines.

Significance: Engagement of the head always excludes disproportion at the brim, as the head is the best pelvimeter. The traditional concept that in primigravidae, the engagement occurs by 38 weeks is not corroborative in clinical practice. In majority, the engagement occurs between 38–42 weeks or even during first stage of labor. In multigravidae, however, the engagement occurs late in first stage of labor after the rupture of the membranes. However, if the head fails to engage in primigravidae even at 38th week, the causes are to be sought for. Common causes are: (1) Deflexed head placing the larger diameter to engage (2) Cephalopelvic disproportion or big head or a combination of both (3) Polyhydramnios (4) Poor formation or yielding of lower uterine segment— preventing the head to sink into the pelvis, (5) Hydrocephalus (6) Placenta previa (7) Pelvic tumors— ovarian or fibroid (8) High pelvic inclination (9) Functional — when no cause can be detected (20%).

Fixed head: The word 'fixed' should not be used to designate an engaged head. Whereas, an engaged head is fixed but conversely, the fixed head is not necessarily engaged. When an egg is placed on the egg cup, it remains fixed yet the maximum diameter does not pass through the rim. Similarly the head may be fixed to the brim but that does not mean that the maximum diameter of the head (biparietal) will pass through the brim.

Vaginal examination

Time: Vaginal examination is done in the antenatal clinic when the patient attends the clinic for the first time before 12 weeks. It is done (1) to diagnose the pregnancy (2) to corroborate the size of the uterus with the period of amenorrhea and (3) to exclude any pelvic pathology. Internal examination is, however, omitted in cases

with previous history of abortion, occasional vaginal bleeding in present pregnancy. Ultrasound examination has replaced routine internal examination. It is more informative and without any known adverse effect.

Procedures: Vaginal examination is done in the antenatal clinic. The patient must empty her bladder

prior to examination and is placed in the dorsal position with the thighs flexed along with the buttocks placed on the footend of the table. Hands are washed with soap and a sterile glove is put on the examining hand (usually right).

Steps:

Inspection: By separating the labia—using the left two fingers (thumb and index), the character of the vaginal discharge, if any, is noted. Presence of cystocele or uterine prolapse or rectocele is to be elicited.

Speculum examination: This should be done prior to bimanual examination especially when the smear for exfoliative cytology or vaginal swab is to be taken. A bivalve speculum is used. The cervix and the vault of the vagina are inspected with the help of good light source placed behind. Cervical smear for exfoliative cytology or a vaginal swab from the upper vagina, in presence of discharge, may be taken.

Bimanual: Two fingers (index and middle) of the right hand are introduced deep into the vagina while separating the labia by left hand. The left hand is now placed suprapubically. Gentle and systematic examination are to be done to note:

(1) Cervix: Consistency, direction and any pathology.

(2) Uterus: Size, shape, position and consistency. Early pregnancy is the best time to correlate accurately uterine size and duration of gestation.

(3) Adnexae: Any mass felt through the fornix. If the introitus is narrow, one finger may be introduced for examination. No attempt should be made to assess the pelvis at this stage.

MATERIALS FOR ACTIVATION OF STUDENTS DURING THE LECTURE: QUESTIONS, SITUATIONAL TASKS, ETC.

QUESTIONS:

- Fundamentals of reproduction: gametogenesis, ovulation, fertilization, implantation.
- Principal events in embryonic and fetal development.
- Development, structure and function of the placenta and fetal membranes.
- Genital tract changes during pregnancy, endocrinology of pregnancy.
- Duration of pregnancy, presumptive, probable and definitive symptoms of pregnancy, chronological appearance of specific signs and symptoms of pregnancy.

- Signs of previous child birth.
- Methods of estimation of gestational age and due date of labor.
- Methods of estimation of fetal weight.
- Obstetrics terminology: lie, presentation, position and attitude of the fetus in the uterus.
- Methods of obstetrical abdominal examination: inspection, palpation, auscultation.

TEST TASKS

Direction: For each of the multiple choice questions select the lettered answer that is the one best response in each case.

1. Worldwide, which of the following is the most common problem during pregnancy?
(A) diabetes
(B) preeclampsia
(C) heart disease
(D) urinary tract infection (UTI)
(E) iron-deficiency anemia

2. A patient presents with a positive pregnancy test, the exact date of the start of her last normal menses, and the date of her luteinizing hormone (LH) surge from a urine kit. Her expected date of delivery can most correctly be calculated by which of the following?
(A) adding 254 to the date of the start of the last menstrual period (LMP)
(B) counting 10 lunar months from the time of ovulation
(C) counting 280 from the first day of the LMP
(D) counting 40 weeks from the last day of the LMP
(E) adding 256 to the date of the elevated urinary LH when detected by home testing

3. A friend mentions to you she just had a positive pregnancy test and wonders if you can tell her when she is likely due. The LMP was June 30. Her expected date of labor is approximately which of the following?
(A) March 23
(B) April 7
(C) March 28
(D) April 23
(E) March 7

4. A patient presents to your clinic complaining of nausea and vomiting. She is currently ingesting combined oral contraceptive pills (OCP) and has used them for over a year. When you tell her she has a positive pregnancy test, she reports that

her last bleeding on the OCPs was 8 weeks ago. In such a situation, determination of the most accurate estimated date of delivery can then be made by which of the following?
(A) eliciting when breast tenderness or morning sickness began
(B) assessing uterine size by physical examination
(C) counting 280 days from the first positive serum pregnancy test
(D) asking the patient when she first felt pregnant
(E) obtaining fetal biometry by ultrasound prior to 20 weeks' gestation

5. Fundal height, part of the obstetric examination, is taken from the top of the symphysis pubis to the top of the fundus. How is it measured?
(A) by calipers, approximating the week of gestation
(B) in inches, approximating the lunar month of gestation
(C) in centimeters and divided by 3.5, approximating the lunar months of gestation
(D) in centimeters, approximating the weeks of gestation beyond 22 weeks
(E) by calipers in centimeters, prognosticating the fetal weight

6. Using your knowledge of normal maternal physiology, which of the following would you employ if a patient at 38 weeks became faint while lying supine on your examination table?
(A) aromatic ammonia spirit (smelling salts)
(B) turning the patient on her side
(C) oxygen by face mask
(D) intravenous (IV) drugs to increase blood pressure
(E) IV saline solution

7. A 19-year-old primigravida with unsure LMP presents to initiate prenatal care. You attempt to estimate gestational age. The uterine fundus is palpable at the level of the pubic symphysis, and fetal heart tones are audible by electronic Doppler. On the basis of this information, what is the approximate gestational age?
(A) 8 weeks
(B) 12 weeks
(C) 16 weeks
(D) 20 weeks
(E) 24 weeks

8. Which of the following nutrients is most likely to be deficient during pregnancy?
(A) iron
(B) vitamin D
(C) vitamin A
(D) calcium

(E) folic acid

9. The relation of the fetal parts to one another determines which of the following?
(A) presentation of the fetus
(B) lie of the fetus
(C) attitude of the fetus
(D) position of the fetus
(E) intention of the fetus

10. A healthy 30-year-old primigravida presents at 34 weeks' gestation. She reports that she has been experiencing abdominal discomfort that increases after eating, especially when in the recumbent position. A series of tests is performed. She has normal vital signs, an unremarkable examination, a fundal height of 33 cm, and a negative urinalysis. Which one of the following represents abnormal test results?
(A) alkaline phosphatase double that of the reference range
(B) hemoglobin of 90 g/L
(C) serum albumin of 35 g/L
(D) serum creatinine level of 80 mmol/L
(E) WBC count of 11, 000/mL

11.The placenta is essential in the growth and development of a healthy fetus. It allows transport of certain things, facilitates transports of others, and is hormonally active. Which of the following statements regarding the placenta is true?
(A) High-molecular-weight substances and protein-bound substances cross readily
(B) In the placenta, fetal blood is in lacunae that bathe maternal capillaries
(C) Infectious organisms cannot cross the placenta from mother to fetus
(D) The placenta fulfills some of the functions of lung, kidney, and intestine for the fetus
(E) The placenta produces only hCG

12. During normal pregnancy a lowered hemoglobin is a physiologic finding. What is its major cause?
(A) low iron stores
(B) blood lost to the placenta and fetus
(C) increased plasma volume
(D) increased cardiac output resulting in greater red-cell destruction
(E) decreased reticulocytosis

13. A 29-year-old primigravida at 36 weeks' gestation complains of dizziness and nausea when reclining to read in bed before retiring at night. Suspecting that her

symptoms are the result of normal physiologic changes of pregnancy, you recommend which of the following?
(A) elevation of both her feet while lying in bed
(B) improved room lighting
(C) mild exercise before retiring to bed
(D) rolling toward the right or left hip while reading
(E) small late night snack

14. The relationship of the long axis of the fetus to the long axis of the mother is called which of the following?
(A) lie
(B) presentation
(C) position
(D) attitude
(E) axis of the conjugate

15. A patient has a profuse, thin, acellular cervical mucus with a high degree of stretchability and a palmleaf crystallization pattern upon drying. Which of the following situations is compatible with this finding?
(A) second trimester of pregnancy
(B) preovulatory estrogen surge
(C) on combination birth control pills
(D) being postmenopausal
(E) the secretory phase of the menstrual cycle

16. The average woman can expect to retain as much as 7 L of water during a normal gestation. What is a major reason for this retention?
(A) decreased venous pressure in the lower fourth of the body
(B) increased plasma oncotic pressure
(C) increased capillary permeability
(D) marked increase in the maternal serum sodium
(E) a physiologic cardiac failure resulting in edema, fluid retention, and enlargement of the heart

17. During pregnancy, blood tests for diabetes are more apt to be abnormal than in the nonpregnant state. Also, nondiabetic women may develop gestational diabetes during the last half of the pregnancy. This is due in part to which of the following?
(A) decreased insulin production
(B) increased food absorption from the GI tract
(C) increased placental lactogen
(D) decreased hepatic secretion of insulin-binding globulin

(E) hemoconcentration

18. During which of the following conditions would the serum prolactin level be greatest?
(A) sleep
(B) ovulation
(C) parturition
(D) menopause
(E) suckling

19. The three principle estrogens in women in decreasing order of potency are
(A) estriol, estradiol, estrone
(B) estrone, estriol, estradiol
(C) estradiol, estrone, estriol
(D) estradiol, estriol, estrone
(E) estriol, estrone, estradiol

20. Which of the following is NOT a presumptive symptom/sign of pregnancy?
(A) cessation of menses
(B) quickening
(C) nausea and vomiting
(D) breast changes
(E) darkening of the skin on the palms of the hands

Answer key

1	E	11	D
2	C	12	C
3	B	13	D
4	E	14	A
5	D	15	B
6	B	16	C
7	B	17	C
8	A	18	C
9	C	19	C
10	B	20	E

LECTURE 2

FETAL DISTRESS. INTRAUTERINE GROWTH RESTRICTION

RELEVANCE: Placenta ("child's place") – is an extremely important organ, which exists only during pregnancy. It connects the functional systems of two organisms – the mother and fetus, providing the fetus with necessary vital substances. Etiology and pathogenesis, clinical features, classification and modern diagnostic methods of placental dysfunction and baby's wellbeing are basic to understand here to provide qualified emergency care, modern principles of prevention and medical rehabilitation of the patients. Unless well studied, this can make impossible to master physiological and pathological obstetric care.

LEARNING OBJECTIVE is to gain basic knowledge about anatomical, physiological and biochemical changes during pregnancy, be familiar with the physiologic adaptations associated with a normal pregnancy, be able to differentiate between certain signs and symptoms that can be common to both disease processes and to physiologic adaptations of pregnancy, obtain knowledge about placenta functions, signs of fetal distress and intrauterine growth restriction, methods of examination of baby's wellbeing, to give appropriate prenatal counseling and supervision in order to provide successful obstetric outcome.

BASIC CONCEPTS: Fertilization and development of a fertilized egg. Placenta, its structure and function. Critical periods of embryo and fetal development. Influence of harmful factors on the embryo and fetus. Physiological changes in a woman's body during pregnancy. Definition, etiology and pathogenesis of placental dysfunction. Classification of placental dysfunction. Evaluation the fetal condition during placental dysfunction depending on the degree of compensatory placental mechanism. Prediction of the course of the pregnancy and the fetal condition depending on the degree of placental dysfunction. definition, etiology and pathogenesis of fetal distress syndrome. Aetiology and pathogenesis of IUGR (retardation, hypotrophy). Hygiene and nutrition of a pregnant woman. Methods of examination of baby's wellbeing. The knowledge of modern methods of diagnostics during the antenatal period during a non-complicated pregnancy helps reveal fetal disorders in the early stages of a pregnancy.

EDUCATIONAL MATERIALS

PLACENTAL DYSFUNCTION. FETAL DISTRESS. INTRAUTERINE GROWTH RESTRICTION

Placenta functions

Placenta ("child's place") – is an extremely important organ, which exists only during pregnancy. It connects the functional systems of two organisms – the mother and fetus, providing the fetus with necessary vital substances. During the course of a normal pregnancy, the placenta is located in the corpus of the uterus on

the posterior (more often) or anterior wall. It is completely formed by 15-16 weeks of pregnancy, after 20 weeks is when active exchange through the placenta vessels begins. From 22 to 36 weeks, the placenta increases in weight, and by 36 weeks it reaches it full functional maturity.

The placenta is similar to a round flat disk. By the end of the pregnancy, the placenta weighs 500-600 gr., has a diameter of 15-18 cm and a thickness - 2-3 cm. There are two surfaces distinguished on the placenta: maternal, turned toward the uterine wall, and the fetal – turned toward the amnion cavity.

Normally, the placenta together with its membranes (afterbirth) is born 10-15 minutes after the birth of the fetus. It is attentively examined and sent for morphological research. First, it is very important to be convinced that the placenta was born (detached) entirely (i.e. there are no damages on its surface and no lobes or parts of the placenta have remained inside the uterine cavity). Secondly, the condition of the placenta can be judged by the course of the pregnancy (whether there was detachment, infectious processes, etc.).

Functions:
Hormons of placenta

Placenta plays the role of an internal secretion gland and synthesizes hormones which provides apropriate growth and development of the fetus.

Placenta produces a variety of hormones of which protein and steroid hormones are significantly important.

Human chorionic gonadotropin (hCG): hCG is a glycoprotein. Its molecular weight is 36000–40000 daltons. It consists of a hormone non-specific **a** (92 amino acids) and a hormone specific **b** (145 amino acids) subunit. hCG is chemically and functionally similar to pituitary luteinizing hormone. The a subunit is biochemically similar to LH, FSH and TSH whereas the b subunit is relatively unique to hCG. Placental GnRH may have a control on hCG formation.

Functions: (1) It acts as a stimulus for the secretion of progesterone by the corpus luteum of pregnancy. The rescue and maintenance of corpus luteum till 6 weeks of pregnancy is the major biological function of hCG.

(2) hCG stimulates Leydig cells of the male fetus to produce testosterone in conjunction with fetal pituitary gonadotropins. It is thus indirectly involved in the development of male external genitalia.

(3) It has got immunosuppressive activity which may inhibit the maternal processes of immunorejection of the fetus as a homograft.

(4) Stimulates both adrenal and placental steroidogenesis.

(5) Stimulates maternal thyroid because of its thyrotropic activity.

(6) Promotes secretion of relaxin from the corpus luteum.

Level of hCG at different periods of pregnancy: hCG is produced by the syncytiotrophoblast of the placenta and secreted into the blood of both mother and fetus. The plasma half life of hCG is about 36 hours. By radioimmunoassay, it can

be detected in the maternal serum or urine as early as 8-9 days postfertilization. In the early pregnancy, the doubling time of hCG concentrations in plasma is 1.4–2 days. The blood and urine values reach maximum levels ranging 100 IU and 200 IU/mL between 60–70 days of pregnancy. The concentration falls slowly reaching a low level of 10–20 IU/ mL between 100–130 days. High levels of hCG could be detected in—(a) multiple pregnancy (b) hydatidiform mole or choriocarcinoma and relatively high in—(c) pregnancy with a 21-trisomy fetus (Down's syndrome). Plasma lower levels are found in ectopic pregnancies and in spontaneous abortion. hCG disappears from the circulation within 2 weeks following delivery.

Human placental lactogen (hPL): This is also known as human chorionic somatomammotropin (hCS). The hormone is synthesized by the syncytiotrophoblast of the placenta. The hormone is chemically and immunologically similar to pituitary growth hormone and prolactin. hPL in maternal serum is first detected during the 3rd week. The level rises progressively from 5 to 25 μg/mL until about 36 weeks. The plasma concentration of hPL is proportional to placental mass.

Functions: hPL antagonises insulin action. High level of maternal insulin helps protein synthesis. hPL causes maternal lipolysis and promotes transfer of glucose and amino acids to the fetus. As a potent angiogenic hormone, it helps to develop fetal vasculature. It promotes growth of breasts for lactation.

Pregnancy associated plasma protein—A (PAPP-A) is secreted by the syncytiotrophoblast. It acts as an immunosuppressant in pregnancy.

Estrogen: In late pregnancy, qualitatively, estriol is the most important amongst the three major estrogens. The site of its production is in the syncytiotrophoblast. The placenta is an incomplete endocrine organ as it has no capability of independent steroidogenesis like that of ovary. For steroidogenesis, it depends much on the precursors derived mainly from the fetal and partly from the maternal sources. Fetal adrenal gland and the placenta contain the complementary enzyme system.

Estriol is first detectable at 9 weeks (0.05 ng/mL) and increases gradually to about 30 ng/mL at term. Fetal death, fetal anomalies (adrenal atrophy, anencephaly, Down's syndrome), hydatidiform moles, placental sulfatase or aromatase deficiency are associated with low estriol.

Progesteron: Before 6 weeks of pregnancy, the corpus luteum secretes 17-ydroxyprogesterone. Following the development of trophoblast, progesterone is synthesized and secreted in increasing amount from the placenta. The daily production rate of progesterone in late normal pregnancy is about 250 mg. Low progesterone levels are observed in ectopic pregnancy and in abortion. High values are observed in hydatidiform mole, Rh-isoimmunization. After delivery, the plasma progesterone decreases rapidly and is not detectable after 24 hours.

Functions of the steroid hormones (estrogen and progesterone):

It is indeed difficult to single out the function of one from the other.

— Together they play an important role in the maintenance of pregnancy. Estrogen causes hypertrophy and hyperplasia of the uterine myometrium, thereby increasing the accommodation capacity and blood flow of the uterus. Progesterone in conjunction with estrogen stimulates growth of the uterus, causes decidual

changes of the endometrium required for implantation and it inhibits myometrial contraction.

— Development and hypertrophy of the breasts during pregnancy are achieved by a number of hormones. Hypertrophy and proliferation of the ducts are due to estrogen, while those of lobulo-alveolar system are due to combined action of estrogen and progesterone (details — below).

— Both the steroids are required for the adaptation of the maternal organs to the constantly increasing demands of the growing fetus.

Progesterone maintains uterine quiescence, by stabilizing lysosomal membranes and inhibiting prostaglandin synthesis. Progesterone and estrogens are antagonistic in the process of labor.

— Estrogens sensitizes the myometrum to oxytocin and prostaglandins. Estrogens ripen the cervix.

— Progesterone along with hCG and decidual cortisol inhibits T-lymphocyte mediated tissue rejection and protects the conceptus.

— Together they cause inhibition of cyclic fluctuating activity of gonadotropin–gonadal axis thereby preserving gonadal function.

Relaxin: It is a peptide hormone structurally related to insulin. The main source of production is the corpus luteum of the ovary but part of it may be also produced by the placenta and decidua. It has been claimed that relaxin relaxes myometrium, the symphysis and sacroiliac joints during pregnancy and also helps in cervical ripening by its biochemical effect.

Gas exchange

Placenta participates in the gas exchange: diffusion of oxygen occurs from the mother's blood to the fetus, and carbonic gas is transported in the opposite direction.

The fetus receives vital substances necessary for its growth and development through the placenta. It is necessary to remember that a lot of substances (alcohol, nicotine, narcotics, many medical preparations, viruses) easily penetrate through the placenta and can harm the fetus. Besides, with the help of the placenta, the fetus gets rid of products of metabolism.

Placenta provides immunological protection for the fetus by detaining the cells of the mother's immune system which, can penetrate to the fetus causing it to be a foreign object and then cause an immune conflict, which could start rejection reactions. At the same time, the placenta passes the maternal antibodies, which protect the fetus from infections.

Placental dysfunction (PD) – a clinical syndrome, caused by morphological and functional changes in the placenta and its infringement of the compensatory-adaptive possibilities. The reasons for placental dysfunction can be infringements of maturing and the formation of the placenta in women with pathologies of the endometrium, ovary-hypophysis and adrenal glands disorders, previous abortions and miscarriages. Pre-eclampsia, risk of miscarriage, overdue pregnancy, iso-serological blood incompatibility of the mother and fetus, genital infantility and

other extra-genital pathologies (dysfunction of the adrenal glands, diabetes, thyrotoxicosis, etc.). play a great role in the occurrence of placental dysfunction, Thus, a complex of transport, trophic, endocrine and metabolic disorders of the placenta can occur, which is the basis for pathology of the fetus and newborn. The degree and character of influence of the pathological condition of the pregnant woman on the fetus depends upon many factors: the term of the pregnancy, the length of influence, condition of compensatory-adaptive mechanisms in the "mother-placenta-fetus" system.

Placental dysfunction – syndrome, caused by morpho-functional changes in the placenta, the result of complex reaction of the placenta and fetus to different pathological conditions in the mother's organism. The basis for the given syndrome is pathological changes in the fetal- and-or uterine-placental complex with infringement of the compensatory-adaptive mechanisms at the molecular, cellular and tissue levels. Thus, a complex of transport, trophic, endocrine and metabolic disorders of the placenta can occur, which is the basis for pathology of the fetus and newborn. The data specifies that the term "feto- or uterine-placental insufficiency", is incomplete because it does not display completely the whole complex of changes in the uterine-placenta-fetus system. In the International Classification of Diseases (ICD-X reviewed in Geneva, 1995) the disease has only one name - "placental insufficiency"; later – placental dysfunction.

Placental ischemia and placental dysfunction are the starting link in the complex chain of pathophysiological mechanisms and progress of gestosis into pre-eclampsia. The condition of the placental complex during a pregnancy is studied completely (hormonal function, uterine-placental blood circulation, activity of the enzymes, ultrasound, tests of the amniotic fluid), especially taking into account the fact that the placenta is a uniform organ, accessible for lifetime pathomorphological research. Changes in the placental complex in pregnant women with different degrees of gestosis allow to track the steps (stages) of formation of placental dysfunction.

No uniform classification of PD exists.

In 1986, M. Ygel offered a classification of placental dysfunction by dividing it into latent placental dysfunction, manifestive and chronic insufficiency. Each division contains minimal, average or severe degree of severity.

In our country, the greatest and most widespread classification of placental dysfunction was offered by M.V. Fedorov and E.P. Kalashnikov (1986), where they distinguish primary (before 16 weeks pregnancy) and secondary (after 16 weeks) PD.

On the basis of the morphological changes in the placenta, I.S. Sidorov and I.O. Makarov (2000), V.I. Kulakov (2004) distinguished compensated, subcompensated, decompensated and critical forms of chronic PD.

Depending on the area of defeat in the placenta, M.V. Fedorov, O.P. Kalashnikov (1986) and H.C. Wallenburg (1990) distinguished relative and absolute placental dysfunction.

V.A. Tsinzerling and co-authors (1998) developed the criteria for morphological diagnostics of the following kinds of functional conditions of the placenta: compensated condition, acute insufficiency, chronic insufficiency with acute decompensation, chronic subcompensated insufficiency, chronic decompensated insufficiency (gradually accruing).

Classification of PD:

I. by the clinical-morphological signs:

a) primary (early) placental insufficiency (before 16 weeks) occurs during the formation of the placenta during implantation, early embryogenesis and placentation under the influence of genetic, endocrine, infectious and other factors. Enzyme insufficiency of the decidual tissue (during dysfunction of the ovaries, anatomical structural disorders, disorders in the location of the placenta attachment, and also defects of vascularization and the problems in the maturing of the chorion) play a valuable role in the development of primary placental dysfunction. Primary insufficiency can assist in the development of congenital disorders of the fetus, stillborn pregnancy. Clinically, it appears as risk of miscarriage in early terms. On occasion, primary placental dysfunction can develop into secondary.

b) secondary (late) placental dysfunction, as a rule, occurs in the late terms of pregnancy, after 16 weeks, under the influence of different maternal factors.

II. by the clinical course:

a) acute – acute disturbances of decidual perfusion and disturbances of the utero-placental blood circulation play a leading role in its development. This kind of placental dysfunction appears as large infarctions of the placenta, preterm detachment of a normally located placenta. As a result, death of the fetus and the termination of the pregnancy can occur quickly.

b) chronic – very frequent pathology (it is observed in approximately every third pregnancy woman in the group of high risk). It can occur in the II trimester and last for a long time.

III. by the condition of the compensatory-adaptive reactions:

a) relative – when the compensatory reactions in the placenta are preserved. Vital support of the fetus is caused by compensatory reactions, which operate on the tissue (increase the number of reabsorbing villa, capillaries of terminal villa, functioning syncytial nodes), cellular and subcellular levels of the syncytiotrophoblast. Infringements of maturing of the placenta and immune disorders have certain value in the development of this type of PD.

b) absolute - most difficult form of chronic PD. It is characterized by the development of damage to the placenta of involution-dystrophic, circulatory and inflammatory character, which is accompanied by the absence of compensatory-adaptive reactions of the chorion at the tissue level.

Diagnostics of disorders of the functions of the placenta.

**1. Determine the degree and character of changes in the placenta. **

a) hormonal researches:

Hormonal methods of diagnostics of PD consist of determining the level of hormones in the amniotic fluid, patient's blood and urine. But, it cannot be limited to the research of one hormone only one time. It is advisable to use dynamic supervision of a complex of hormones in the placental complex, placental lactogen (PL) and chorionic gonadotropin (CG) – to diagnose the condition of the syncytiotrophoblast of the placenta; estrogen (estradiol-E2 and estriol-E3) – to evaluate the function of the placental complex; progesterone (Pg)-to diagnose the condition of the uterine-placental-fetal system (see table 1).

2. Determine the condition of the fetus and placental system.

a) measure the height of the uterine fundus over the pubis symphysis and the circumference of the abdomen in dynamics.

Special attention should be paid during external measurement in the II and beginning of the III trimester when the received sizes are comparison to the term of the pregnancy, which shows any fetal growth retardation. It is convenient to use a gravidogram, where normal measurements of the height of the uterus fundus are marked. The lack of 20 mm in the size of the uterus or more at 32-33 weeks is basis for considering the presence of hypotrophy of the fetus.

b) determine the sizes of the fetus with an ultrasound.

c) study the respiratory activity of the fetus with an ultrasound.

d) determine the movement activity of the fetus with an ultrasound.

It is performed at 7-8 weeks of pregnancy, but its evaluation has the greatest value in the III trimester when the fetus does 5 and more movements in 30 minutes. Thus, an increase in general movement activity of the fetus is considered compensatory reactions, a decrease - an adverse sign.

e) ultrasound of the urinary functions of the kidneys of the fetus by the amount of excreted urine.

The latter is determined by the difference between the volume of the urinary bladder during the first US and the repeated US in 1 hour. The given test is especially valuable when diagnosing hypotrophy of the fetus, during which the excretion of the urine decreases to 15-18 ml (normal – 24-27 ml). Also consider, that a decrease in the speed of urine excretion of the fetus is observed during gestosis of the pregnant women, in those cases there is no growth retardation by data from the US. The degree of decrease in the production of urine is directly dependant on the severity of gestosis, which is connected not only to fetal growth retardation, but also to the infringement in the regulation of the kidney functions.

f) evaluation of the fetal heart activity.

Along with auscultation, the most accessible and widespread method of evaluating the fetal heart activity is cardiotocography, registration of fetal heart rate (HR). Cardiomonitoring shows initial and expressed signs of suffering of the fetus as a result of fetal distress.

The basic treatment for placental dysfunction:

1) Improving the uterine-placental blood circulation;

2) Normalizing the gas exchange between the mother and fetus;

3) Improving the metabolic functions of the placenta;

4) Acting on the fetus, through the placenta and using the para-placental way of exchange.

Different methods and different means influence multiple functions of the placenta at once. Normalizing the uterine-placental blood flow, certainly, improves the transport of nutrients and gas exchange, which is an important factor in the synthesis of hormones. Correcting the metabolic changes leads to the improvement of gas exchange and normal function of the placenta which in turn, improves the haemodynamics of the placenta.

Normalizing the uterine-placental blood flow is the basic link in normalizing the function of the placenta; it is achieved by using vasodilating means or preparations which relax the uterus, along with actions directed on normalizing the reocoagulate properties of the blood:

a) physical methods of action (electro-relaxation of the uterus, electrophoresis of magnesium, thermal procedures on the renal area, diathermy, inductothermy, etc.) reflex the biometry and lead to the dilation of vessels;

b) abdominal decompression removes extra muscle work of the uterus by overcoming of the tonus of the abdominal muscles. It leads to an increase in blood flow in the uterus and improves placental perfusion. Besides that, it leads to an increase in the synthesis of estriol and an increase in the transport function of the placenta;

c) hyperbaric oxygenation is applied to improve the function of the placenta and fetal condition, especially in pregnant women heart disorders. It preserves the activity of the respiratory enzymes, assists in normalizing the carbohydrate metabolis;

medicament means. Aminophylline or teophylline, vasodilating substances, are used; they can be introduced by i\v by stream or droplet introduction. Complamin, teonicole are used for the same purposes. It should be noted that hypersensibility is possible in pregnant woman and so individual doses of complamin should be selected. Considerable improvement in the uterine-placental blood circulation causes vaso-active preparation trental. It has vasodilating action, decreases the resistance of peripheral vessels, increases the collateral blood circulation. The preparation improves the rheological properties of blood and microcirculation, and it can be used in hospitals and female consultations.

Prevention of placental dysfunction

1) eliminating the influence of harmful factors during the period before conception and especially during the first days and weeks of pregnancy:

a) eliminating smoking, alcohol, taking of medicines (without prescription from the doctor);

b) before pregnancy (and during pregnancy) sanation of sites of infection, treatment of chronic diseases.

2) after the patient becomes pregnant, it is necessary to explain to her the role of high-grade balanced food, high-grade and extra sleep.

3) finding the group of high risks and registering them for regular medical check-ups.

Fetal distress

All disorders of the functional state of the fetus are defined by the term "fetal distress"

Pathogenesis of fetal distress.

The main pathogenetic factor that leads to impaired functions of the fetal body, metabolic processes, and the occurrence of a terminal state of the fetus is oxygen deficiency.

Fetal condition disorders during pregnancy and childbirth occur against the background of various complications on the part of both the pregnant woman and the fetoplacental complex.

There are four main groups of factors that can cause fetal distress.

Risk factors for fetal distress

1. Pathological conditions that lead to impaired oxygen transport to the uterus:

• Impaired oxygenation of maternal blood (cardiovascular and pulmonary pathology, generalized angiopathies in diabetes mellitus, infectious diseases, the influence of harmful environmental factors and bad habits);

• Hemic hypoxia in the mother (anemia of pregnant women);

• Circulatory disorders in the mother (hypotension, hypertensive disorders of pregnancy, preeclampsia).

2. Pathological conditions that disrupt oxygen exchange between the uterus and the placenta:

• Pathological changes in spiral arterioles as a result of inflammatory diseases of the endometrium and abortions transferred before pregnancy;

• Occlusive lesions of spiral arterioles as a result of microthrombosis, peripheral vasospasm (preeclampsia, post-pregnancy);

• Anomalies of labor activity.

3. Placental factors themselves:

• Disorders of the development and maturation of the placenta (angiomas, placental cysts, bipartite placenta, etc.)

4. Pathological conditions of the fetus and umbilical cord:

• Disorders of umbilical blood circulation (umbilical cord entanglement and knots)

• Fetal diseases (hemolytic fetal disease, malformations, etc.).

Methods for diagnosing fetal distress:

1. Auscultation of cardiac activity (from 20 weeks of pregnancy) - determination of the fetal heart rate in one minute:

- physiological norm - 110 - 170 beats / min

- heart rate more than 170 beats / min and less than 110 beats / min indicates fetal distress.

2. Fetal biophysical profile (FBP) (from 30 weeks of pregnancy) - the sum of the scores of individual biophysical parameters is assessed (fetal respiratory movements, fetal tone, fetal motor activity, fetal cardiac reactivity to a non-stress test (NST), amniotic fluid volume).

Modified FBP evaluates only two parameters - a non-stress test and the amount of fluid. Two methods are used to assess the amount of amniotic fluid. The first is the assessment of the maximum depth of the vertical pocket (it indicates a pocket depth of 2-8 cm as normal, 1-2 cm as borderline, less than 2 cm as low (oligohydramnios), more than 8 cm as high (polyhydramnios)).

The second method is the assessment of the amniotic fluid index (the sum of the deepest vertical pockets of fluid in the four quadrants of the uterus, with the navel as the central point).

3. Dopplerometry of blood flow velocity in the umbilical artery (reflects the state of microcirculation in the fetal part of the placenta, the vascular resistance of which plays a major role in fetoplacental hemodynamics).

Diagnostic criteria:

• Normal blood flow – high diastolic component on the Doppler in relation to the isoline, the ratio of the amplitude of systole to diastole is no more than 3.

• Pathological blood flow:

1. Slowed blood flow – decrease in the diastolic component, the ratio of the amplitude of systole to diastole is more than 3.

2. Terminal blood flow (indicating a high probability of antenatal fetal death):

• Zero – blood flow in the diastole phase stops (there is no diastolic component on the Doppler)

• Negative (reverse, reverse) – blood flow in the diastole phase takes on the opposite direction (on the Doppler, the diastolic component is below the isoline)

Diagnostics

1) Auscultation of fetal heart activity at each visit to the obstetrician-gynecologist or midwife.

2) If the heart rate is more than 170 beats/min and less than 110 beats/min, which indicates fetal distress, there is a need to assess the biophysical modified or extended fetal bioprofile.

3) In case of pathological BPP, dopplerometry of blood flow in the umbilical artery is performed. In case of normal blood flow in the umbilical artery, repeated BPP is necessary after 24 hours.

4) In case of pathological blood flow in the umbilical artery - hospitalization in a maternity hospital of the III level of care.

Tactics of managing pregnancy with fetal distress

1. Hospitalization of a pregnant woman to a maternity hospital or a department of pregnancy pathology is indicated if, according to the data of the BPP study and/or Doppler blood flow measurement, there is: pathological assessment of BPP (6 points and below); repeated (after 24 hours) questionable assessment of BPP (7-8 points); slowed diastolic blood flow in the umbilical arteries; critical changes in blood flow in the umbilical arteries (zero and reverse).

2. Treatment of concomitant diseases of the pregnant woman that lead to fetal distress.

3. Staged dynamic monitoring of the fetus.

4. Prolongation of pregnancy to term is possible with normal BPP and Doppler fetal blood flow measurements.

5. In case of slow diastolic blood flow in the umbilical arteries, a study of the fetal biophysical profile (BPP) should be performed:

• in the absence of pathological BPP indicators, repeated Dopplerometry should be performed with an interval of 5-7 days;

• in the presence of pathological BPP indicators, Dopplerometry should be performed at least once every 2 days and BPP daily.

6. Detection of deterioration of fetal blood flow indicators (occurrence of constant zero or negative blood circulation in the umbilical arteries) is an indication for emergency delivery by cesarean section.

Tactics of treatment of pregnant women with fetal distress.

Up to 30 weeks of pregnancy, treatment of concomitant diseases in a woman that led to fetal distress.

After 30 weeks of pregnancy, the most effective and justified method of treating fetal distress is timely delivery.

Delivery of pregnant women with fetal distress.

1. Natural birth can be performed (under cardiomonitoring of the fetus) in the following cases: normal or slow blood flow in the umbilical arteries, if there is no fetal distress (BPP score of 6 points or lower);

2. Indications for emergency delivery by cesarean section after 30 weeks of pregnancy are:

• critical changes in blood flow in the umbilical arteries (zero and reverse);

• acute fetal distress (pathological bradycardia and decelerations of the heart rate regardless of the type of blood flow (normal or slow) in the umbilical arteries during pregnancy);

• pathological BPP (score 4 points and below) in the absence of biological maturity of the cervix

Diagnosis of fetal distress during labor

1. Auscultation of the fetal heartbeat: pathological heart rate (>170 beats/min. or <110 beats/min.)

2. Cardiotocography (CTG):

• tachycardia or bradycardia;

• stable rhythm monotony (recording width 5 beats/min. or less);

• early, variable and especially late decelerations with an amplitude of more than 30 beats/min.;

• sinusoidal rhythm more than 40% of the recording.

3. Determination of meconium in amniotic fluid in case of rupture of the amniotic sac.

The presence of thick meconium in the amniotic fluid in combination with pathological changes in the fetal heart rate is an indication for urgent delivery in cephalic presentation of the fetus.

Tactics of labor in case of fetal distress

1. Avoid the supine position of the mother

2. Stop the administration of oxytocin, if it was previously prescribed.

3. If the cause of the pathological fetal heart rate is the mother's condition, appropriate treatment should be carried out.

4. If the mother's condition is not the cause of the pathological fetal heart rate, and the fetal heart rate remains pathological during the last three contractions, an internal obstetric examination should be performed to determine the obstetric situation and clarify the possible causes of fetal distress.

5. When diagnosing “fetal distress”, urgent delivery is necessary:

• in the first stage of labor - cesarean section;

• in the second stage of labor: in cephalic presentation - vacuum extraction or obstetric forceps; in breech presentation - extraction of the fetus by the pelvic end.

Fetal Growth Retardation (FGR)

Fetal growth retardation (FGR) is defined as the failure of the fetus to reach its growth potential due to pathological factors, most commonly placental dysfunction. Worldwide, FGR is a leading cause of stillbirth, neonatal mortality, and short- and long-term morbidity.

A *fetus is considered small for gestational age* (SGA) if the estimated fetal weight (EFW) or birth weight is less than the 10th percentile for gestational age.

Risks associated with fetal growth retardation.

Antenatal

• Stillbirth
• Preeclampsia
• Placental abruption
• Preterm labor

Neonatal (short-term)

• Neonatal mortality
• Neonatal morbidity (hypoglycemia, hyperbilirubinemia, hypothermia, necrotizing enterocolitis, respiratory morbidity, intraventricular hemorrhage)

Neonatal (long-term)

• Psychomotor developmental disorders

• Metabolic syndrome (obesity, hypertension, diabetes mellitus, cardiovascular disease)

Common etiological factors of fetal growth retardation.

Suboptimal uteroplacental perfusion and fetal nutrition

a. Maternal (preplacental) factors

• Hypoxemia (chronic lung disease, high altitude)

• Anemia

• Smoking, substance abuse (cocaine, methamphetamine)

• Malabsorption, poor weight gain

• Environmental toxins: air pollution, heavy metals (lead, mercury), perfluorooctanoic acid

b. Placental factors

• Pathology associated with maternal malperfusion (infarctions, fibrin deposits, chronic detachment)

• Pathology associated with fetal malperfusion

• Chronic inflammation of the placenta (e.g., villitis of unknown etiology)

• Limited placental mosaicism

c. Umbilical (postplacental) factors

• Excessive twisting of the umbilical vessels

• Increased length of the umbilical cord

• True umbilical knot

• Single umbilical artery

• Marginal or membranous attachment of the umbilical cord

Fetal pathology

• Genetic disorders (chromosomal, microdeletions/duplications, monogenic diseases, epigenetic disorders)

• Structural abnormalities (e.g., congenital heart defects, gastroschisis)

• Congenital infections (cytomegalovirus, toxoplasmosis, herpes, rubella, syphilis, Zika virus, malaria)

• Exposure to teratogens (drugs, toxins)

Risk factors for fetal growth retardation.

a. *Anamnestic risk factors*

Maternal demographics

• Older age
• Underweight
• Living at high altitude
• Severe anemia, hemoglobinopathies
• Environmental factors (air pollution, heavy metals, high temperatures)

b. Medical conditions

• Chronic hypertension
• Chronic kidney disease
• Systemic lupus erythematosus
• Inflammatory bowel disease
• Antiphospholipid syndrome
• Pregestational diabetes (long-standing)

c. Obstetric history

• Previous pregnancy with preeclampsia or preeclampsia

Biochemical markers

• Low PlGF
• Low PAPP-A
• High alpha-fetoprotein

Ultrasound markers

• Uterine arteries: pulsatility index > 95th percentile
• Uterine arteries: bilateral dicrotic notch
• Marginal or membranous cord attachment
• Two umbilical vessels (single umbilical artery)
• Abnormal placental morphologya
• Reduced fetal growth rate

CLASSIFICATION OF FETAL GROWTH RETARDATION

Early FGR (< 32 weeks)	**Late FGR (≥ 32 weeks)**
• EFW or AC <3rd percentile • or	• EFW or AC <3rd percentile • or • • ≥2 of the following 3 criteria: • a. EFW or AC <10th percentile

• AP with zero end-diastolic blood flow velocity; RRV — reverse end-diastolic blood flow velocity • or • • EFW or AC <10th percentile combined with one or more of the following: • a. AP PI >95th percentile • b. MA PI >95th percentile	• b. EFW or AC percentiles decrease >2 quartiles at growth percentiles • c. CPR <5th percentile or PI • AP >95th percentile

Early FGR, with a prevalence of 0.5–1%, is usually severe and is more frequently associated with abnormal Doppler findings in the AP than late FGR. The placental pathology underlying early FGR is often similar to that seen in early preeclampsia (maternal vascular malperfusion), which explains the close association of early FGR with preeclampsia. The main challenge in early FGR is management (i.e., timing of delivery), attempting to find the optimal balance between the competing risks of stillbirth and prematurity.

Late FGR is more common than early FGR, with a prevalence of 5–10%. In contrast to early FGR, it is usually milder, less frequently associated with preeclampsia, and is usually associated with normal Doppler findings in the umbilical arteries. The diagnosis of late FGR is mainly based on adaptive changes in cerebral blood flow ("redistribution" or "brain protection effect"), reflected in low resistance to blood flow in the SMA. Given that in late FGR, Doppler values in the umbilical arteries and the ductus venosus usually remain within normal limits, the natural history in these cases is less predictable, and there is a risk of sudden decompensation and stillbirth.

DIAGNOSIS OF FETAL GROWTH RETARDATION

1. Measurement of fundal height (SFH).

SFH measured with the woman in the supine position using a non-elastic tape measure after she has emptied her bladder. The SFH is defined as the distance from the superior border of the symphysis pubis to the fundus of the uterus. The SFH, measured in cm between 24 and 38 weeks of pregnancy, approximates gestational age. Factors such as maternal obesity, uterine leiomyoma, and polyhydramnios may further limit the accuracy of the SFH as a screening tool.

2. Ultrasound determination of fetal weight (Estimated Fetal Weight)

Standard fetal biometrics include the assessment of the chest circumfrence, biparietal diameter, AC, and FL. Fetal weight is estimated based on various combinations of the four biometrics mentioned above, using one of many published formulas. The accuracy of most formulas is in the range of ±10%, and the error has been shown to be greater at extreme values of fetal weight, and the accuracy of the

estimate is also affected by factors such as fetal sex, presentation, and multiple gestation (greater in twin pregnancies).

Management of pregnancy with fetal growth restriction

Recommendations for monitoring, timing and method of delivery in cases of suspected ectopic pregnancy

Data received	Risk of stillbirth	Suggestions for monitoring	Timing and method of delivery
SGA(EFW within the 3-9th percentile, normal water content and Doppler results)	Low	• Doppler (UCA, MCA) every 1-2 weeks • Fetometry every 2 weeks • At ≥37 weeks, consider performing BFP/NST 1-2 times a week	• 37–39 weeks • Delivery method: induction of labor
Uncomplicated FGR < 3rd percentile (normal water content and Doppler findings)	Low	• Doppler (UCA, MCA) every 1-2 weeks • Fetometry every 2 weeks • At ≥37 weeks, consider performing BFP/NST 1-2 times a week	• 36–38 weeks • Delivery method: induction of labor
FGR with moderate pathological changes: • Early Doppler changes: a. UCD PI>95 percentile, or b. MCA PI 95 percentile • Oligohydramnios • Suboptimal growth interval • Suspected preeclampsia	Low	• Consider inpatient monitoring • Consider corticosteroids for fetal lung maturation • BFP/NST 1-2 times per week • Doppler (UCA, MCA, DV) 1-2 times per week • Fetometry every 2 weeks	• 34–37 weeks • Method of delivery: cesarean section or induction of labor
FGR with zero end-diastolic blood flow velocity and reversed end-diastolic blood flow velocity	• General risk of stillbirth: a. zero end-diastolic blood flow velocity 6.8%, relative risk 3,6 (2,3–5,6) b. reversed end-diastolic blood flow	• Monitoring in a hospital setting • Corticosteroids for fetal lung maturation • BFP/NST 1-2 times a day • Doppler (UC, MCA, DV) every 1-2 days	• zero end-diastolic blood flow velocity: 32–34 weeks • reversed end-diastolic blood flow velocity: 30–32 weeks

	velocity 19%, relative risk 7,3 (4,6–11,4) • Risk of stillbirth when following a clear monitoring protocol with a safety net: a. zero end-diastolic blood flow velocity: 0–1% b. reversed end-diastolic blood flow velocity: 1–2% • Average time to deterioration: a. zero end-diastolic blood flow velocity: 5 days b. reversed end-diastolic blood flow velocity: 2 days	• Fetometry every 2 weeks	• Method of delivery: cesarean section
FGR with pathological Dopplerometry in the DV	• Overall risk of stillbirth: 20%, relative risk 11,6 (6,3–19,7) • Risk of stillbirth when following a clear monitoring protocol with a safety neta. The increased pulsatility index in the venous duct :2% b. Null/reverse A-wave in the ductus venosus: 4%	• Monitoring in a hospital setting • Corticosteroids for fetal lung maturation • BFP/NST 1-2 times a day • Doppler (UC, MCA, DV) daily	• 26–30 weeks • Delivery method: Caesarean section

MATERIALS FOR ACTIVATION OF STUDENTS DURING THE LECTURE: QUESTIONS, SITUATIONAL TASKS, ETC.

1. A 28-year-old pregnant woman, gestational age 37 weeks. The pregnant woman smokes a lot, her husband is healthy. No extragenital pathology was detected in the pregnant woman. Objectively: fetal heartbeat – 126 beats/min, muffled. According to ultrasound, the fetal dimensions correspond to a 34-week pregnancy. 1. What is the most likely reason for the discrepancy between the fetus and the gestational age?

   A. Genetic pathology

   B. Fetoplacental insufficiency

   C. Fetal hypoxia

   D. Hormonal insufficiency

   E. Age of the pregnant woman

2. A 32-year-old primiparous woman is in labor. The fetal head is in the pelvic cavity. The fetal heartbeat has started to slow down, and arrhythmia has appeared. What is correct managment?

A. Application of exit forceps.

B. Application of vacuum extractor.

C. Emergency cesarean section.

D. Episiotomy.

E. Application of high forceps.

3. In a 30-year-old primiparous woman, labor lasts 4 hours. The labor is term. Contractions last 30-35 seconds, after 5 minutes. Meconium waters have come out. Fetal heartbeat - 90 beats per minute. During vaginal examination: the cervix is smoothed, the opening of the external cervical os is 3 cm, the fetal head is in the plane of the entrance to the small pelvis. What actions are most appropriate?

A. Drug-induced sleep.

B. Obstetric forceps.

C. Emergency cesarean section.

D. Administration of uterotonics.

E. Administration of antispasmodics

4. In a primigravida 35-year-old woman at 37 weeks of gestation, according to ultrasound examination, the fetal dimensions correspond to 32 weeks of gestation, fetal mobility and muscle tone are reduced, and the duration of respiratory movements is reduced. What is the obstetric tactic?

A. Urgent delivery

B. Administration of vasoactive drugs

C. Administration of tocolytics

D. Conducting a non-stress test

E. Monitoring over time

5. Primiparous woman, 36 years old, labor lasts 5 hours. Labor is term. Contractions last 35-40 seconds after 5 minutes. Meconium-stained water has passed. Fetal heartbeat - 90 beats per minute. During vaginal examination: The cervix is smoothed, the opening of the cervix is 6 cm. What actions are most appropriate?

A. Cesarean section.

B. Obstetrics forceps

C. Drug-induced sleep

B. Administration of uterotonic drugs

E. Antispasmodic administration

Questions for self-control on the topic:

1. What is the definition of placental dysfunction?

2. What is the classification of placental dysfunction?

3. What are the current views on risk factors and pathogenesis of placental dysfunction?

4. What does the term “fetal growth retardation” mean and on the basis of what methods is it possible to diagnose FGR?

5. What methods are used to diagnose the functional state of the fetus in FGR?

6. By what criteria is the condition of the fetus assessed when studying its biophysical profile?

7. What is the strategy for managing pregnancy and childbirth with FGR?

8. What is the term “fetal distress”?

9. What methods are used to diagnose fetal distress during pregnancy and childbirth?

10. What heart rate parameters during cardiotocographic examination indicate the presence of fetal distress during childbirth?

11. What is the strategy for managing pregnancy and childbirth when determining fetal distress?

12. How is emergency delivery performed in case of fetal distress during labor?

13. How to prevent the development of placental dysfunction in the pre-pregnancy stage.

LECTURE 3
«Miscarriage»

TOPIC RELEVANCE

Preterm birth is the single most important factor effecting perinatal outcomes in terms of morbidity and mortality. Preterm labor is defined by WHO as the onset of regular uterine contractions, between viability and 37 weeks' gestation, associated with cervical effacement and dilatation. Current guidelines from many progressive countries describe a "threshold of viability' between 22 and 26 weeks; thus, preterm birth occurs between 22-26 weeks and 37 weeks' gestation. Up to 30-40% of cases of preterm birth are iatrogenic due to deliberate induction of labor or pre labor caesarean section for conditions causing maternal or fetal compromise. The remainder of the cases of preterm birth follow spontaneous preterm labor, with or without preterm prelabor membrane rapture, and the initiating factors are the subject of much scientific interest and debate.

LEARNING OBJECTIVE is to gain basic knowledge about definition of preterm labor and delivery, current concepts in the pathophysiology of preterm labor, risk factors for preterm labor: obstetrics history infection, demographics, psychosocial factors, long term prediction of preterm labor: fetal fibronectins, cervical length, inflammatory markers risk scoring systems, management of preterm labor: tocolysis use of corticosteroids, antibiotics, prevention of preterm labor: progesterone, cervical cerclage, obstetrics issues in preterm labor: mode of delivery, care of premature neonate, methods of obstetrical abdominal examination: inspection, palpation, auscultation in order to provide successful obstetric outcome.

BASIC CONCEPTS: Causes of spontaneous abortion at different gestational ages. Classification, symptoms, diagnosis, treatment and prevention of spontaneous abortion. Cervical insufficiency: diagnosis, management. Prevention of miscarriage. Preterm labor: causes, prediction, diagnosis, management. Management of PPROM. Prevention of preterm delivery.

EDUCATIONAL MATERIALS

Epidemiology Definitions

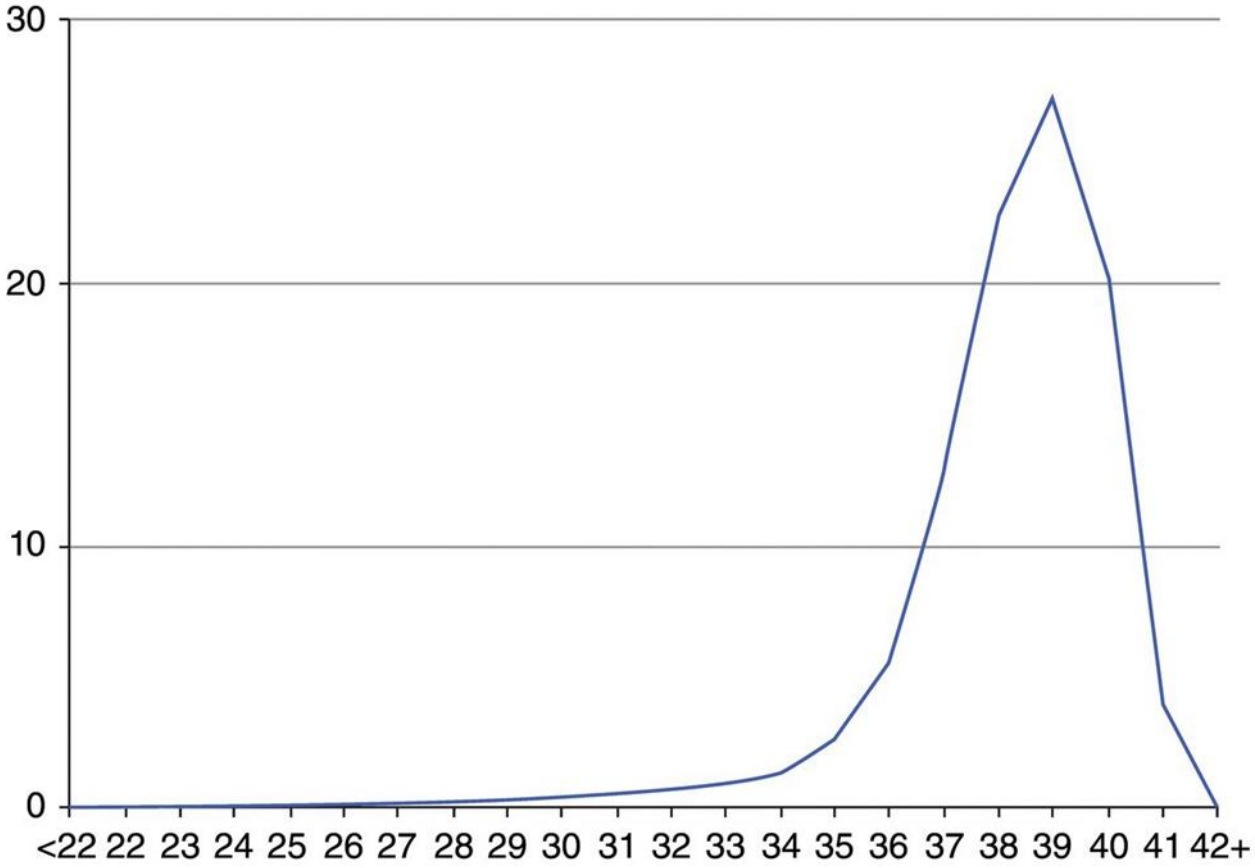
Preterm birth is defined as delivery of a baby before 37 completed weeks of pregnancy. Legally, in the UK, the 1992 Amendment to the Infant Life Preservation Act defined the limit of viability as 24 weeks. However, a small number of infants born at 23 weeks will survive. Mortality in preterm babies born after 32 weeks' gestation is similar to that of babies born at term. The risk of neonatal mortality or survival with handicap becomes significant in very preterm infants (defined as those born between 28 and 32 weeks) but is most significant in extremely preterm infants (defined as those born before 28 weeks). In modern obstetric practice assessment of gestational age is based principally on fetal biometry measured by first- or second-trimester ultrasound rather than the date of the last menstrual period. However, in the past, assessment of gestational age was not always accurate and paediatric statistics were based on birthweight rather than gestational age data. Low birthweight is defined as less than 2.25 kg, very low birthweight as less than 1.5 kg

and extremely low birthweight as less than 1 kg. Using these definitions to describe outcome data leads to blurring of the distinction between preterm babies and small-for-gestational-age babies, particularly in the low birthweight category, and also fails to differentiate the normally grown preterm neonate from the neonate who is both preterm and small for gestational age.

Incidence

Globally, about 15 million babies are born preterm each year. The incidence of preterm birth varies significantly across the globe. In most developed nations the rate of preterm birth is below 10%, the UK rate is around 7% and in the USA the rate fluctuates between 9 and 12% with huge geographical or interstate variation. Countries with preterm birth rates exceeding 15% include Malawi, Congo, Comoros, Zimbabwe, Equatorial Guinea, Mozambique, Gabon, Pakistan, Indonesia, Mauritania and Botswana. The greatest numbers of preterm births occur in India, China, Nigeria, Pakistan, Indonesia and the USA. Preterm birth rates are increasing in almost all countries with reliable data. Especially in the developed world, this is associated with assisted reproduction increasing the rates of multiple pregnancy and an increased tendency to obstetric intervention. Strategies in the USA to encourage obstetricians to reduce their reliance on elective preterm delivery to manage conditions such as growth restriction and pre-eclampsia have been associated with a significant local reduction in the preterm birth rate, although this applies largely to late preterm births. The proportion of preterm births in each gestation or age week époque increases almost exponentially from about 32 weeks. This means that the great majority of preterm births occur at later gestations. In England some 15% of all preterm births occur before 32 weeks, whilst 70% occur between 35 and 37 weeks (Fig. 28.2). The UK rate of preterm birth prior to 32 weeks has remained relatively stable at 1–2%. About one-quarter of preterm births are elective deliveries, usually for pre-eclampsia, intrauterine growth restriction or maternal disease. The remainder is due to preterm labor and delivery.

Fig. 28.2 Live birth percentages by gestation, 2011 birth cohort, England and Wales. *Source:* UK Office for National Statistics.

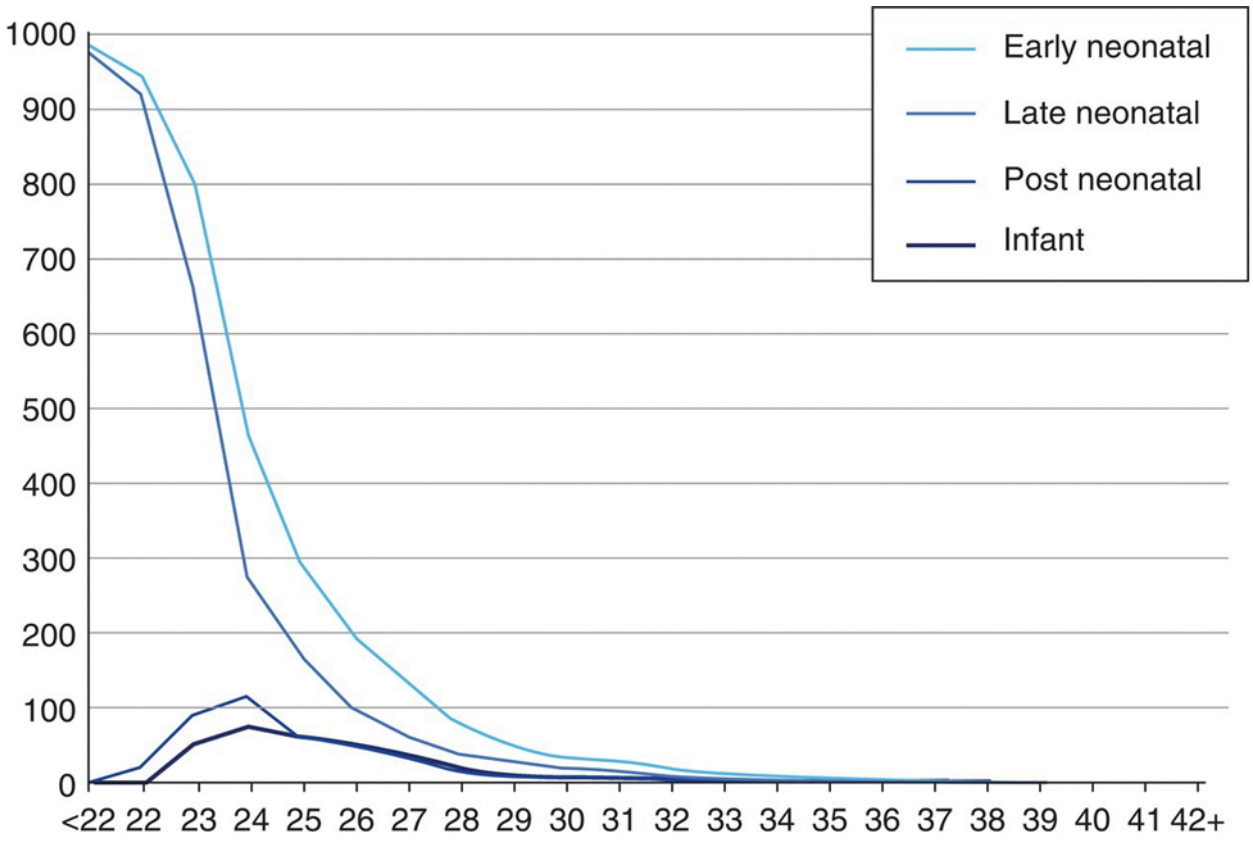


The incidence of spontaneous preterm labour is at its lowest in women in their twenties. The risk is increased in teenagers and in women aged over 30. There is a higher incidence of preterm labour in first pregnancies. Higher parity alone is not a risk factor for preterm labour. Indeed there is a progressively lower risk with each successive term birth. Marital status, cigarette smoking, environmental stress, poor nutrition and use of alcohol, coffee and street drugs (especially cocaine) have all been linked to an increased risk of preterm birth. However, many of these factors are interlinked and all are factors associated with social disadvantage. There does appear to be an association between race and risk of preterm delivery. In the UK the risk of preterm birth is 6% in white Europeans but 10% in Africans or Afro-Caribbean's, although it is difficult to differentiate genetic variation from social deprivation. In studies of populations where black and white women have similar lifestyles, levels of income and access to medical care (e.g. in US Army personnel), preterm delivery rates show a less marked ethnic variation. However, the identification of specific genetic polymorphisms that increase the risk of preterm labor does suggest that genetic as well as environmental factors may be involved, which explains the increased risk of preterm labor in certain ethnic populations. Intervention studies have shown that antenatal smoking cessation programmers reduce the risk of preterm birth, although there is no evidence currently that other interventions, such as increased frequency of antenatal care, dietary advice or an increase in social support, reduces the risk of preterm labor.

Neonatal outcomes after preterm birth

As of 2014, preterm births became the single largest cause of death of children under the age of 5 throughout the world. Of the 6.3 million children who died before the age of 5 years in 2013, 52% died from infection and 44% died in the neonatal period. The three leading causes of death were complications of preterm birth (15.4%), pneumonia (14.9%) and complications of labor and delivery (10.5%). Previously infection had been the largest cause of death in this age group but global improvements in the management of pneumonia, diarrhea and measles since the turn of the century has substantially reduced the impact of these diseases on childhood mortality. Globally, there are dramatic differences in survival rates for preterm infants depending on where they are born. Over 90% of extremely preterm babies (<28 weeks) born in low-income countries die within the first few days of life, while less than 10% of babies born at this gestation die in high-income settings, a 10 : 90 survival gap. The risk of a neonatal death due to complications of preterm birth is more than 12-fold higher for an African baby than for a European baby. In developed nations, and in particular the UK, survival rates for preterm babies have improved steadily over the past three decades principally due to the introduction of surfactant therapy, improvements in neonatal respiratory management and more widespread use of antenatal steroids (Fig. 28.3). The Epicure study, which examined extremely preterm infants born in 1995, reported mortality rates of 100%, 90% and 80% for preterm infants admitted to neonatal units at 21, 22 and 23 weeks gestation, respectively. The subsequent Epicure II study repeated this exercise in a similar cohort born in 2006 and found that although rates of survival of babies born between 22 and 25 weeks gestation has increased since 1995, the pattern of major neonatal morbidity and the proportion of survivors affected are unchanged. Therefore, improved survival for very preterm infants has been associated with an increase in the proportion of children with cerebral palsy who were born preterm. Neonatal mortality rises gradually between 32 and 28 weeks, from 2 to 8%, and then more dramatically and exponentially to 80% at 23 weeks.

Fig. 28.3 Infant mortality rate by gestation, 2011 birth cohort, England and Wales. *Source:* UK Office for National Statistics.

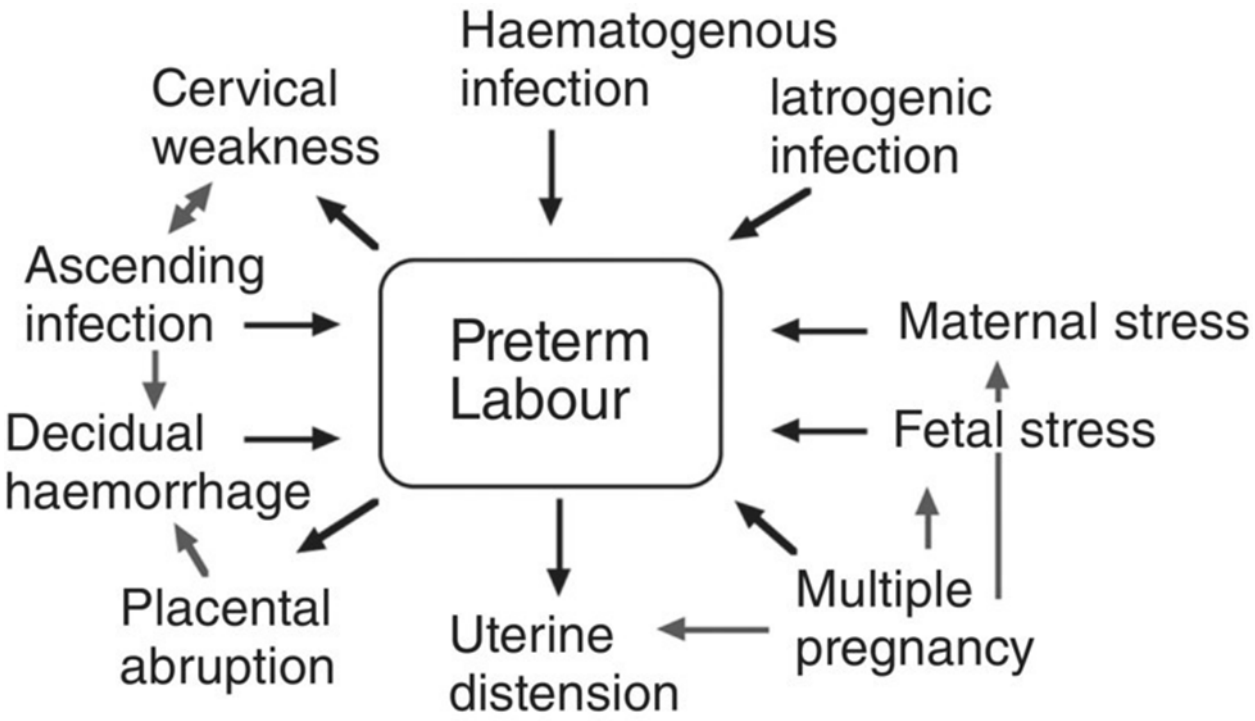


In the past, surfactant deficiency leading to neonatal respiratory distress syndrome (RDS) was the major cause of morbidity and mortality in preterm infants. Alveolar surfactant production begins at 30–32 weeks' gestation. Therefore, preterm infants born prior to 30 weeks are at highest risk. The impact of RDS on neonatal morbidity and mortality has been dramatically reduced in the past three decades through use of antenatal corticosteroids and exogenous surfactant replacement. The risk of chronic lung disease, defined as a need for ventilation or oxygen supplementation at 36 weeks after conception, has however continued to rise because of the increased survival of extremely preterm infants. The fetal and neonatal brain is especially susceptible to injury between 20 and 34 weeks. The greatest risk of long- term neurodevelopmental problems is in infants born before 28 weeks or at birthweights of less than 1000 g. The Epicure study showed that in infants born before 26 weeks' gestation, approximately half had some disability at 30 months and approximately one-quarter had severe disability. Cerebral palsy may be related to periventricular hemorrhage, post- hemorrhagic hydrocephalus and periventricular leukomalacia. Hypoxia–ischemia is a major risk factor for neonatal cerebral damage. However, there is growing evidence for a strong link between chorioamnionitis, fetal inflammation and the risk of periventricular leukomalacia. The overall risk of cerebral palsy associated with preterm birth at any gestational age (i.e. 23–36 weeks) is increased sevenfold over that of babies born at term; however, with decreasing gestational age this risk increases dramatically, with relative risks of 14, 46 and 70-fold, in infants born before 34, 31 and 28 weeks, respectively. The risk of visual impairment due to retinopathy of prematurity is

inversely related to gestational age at birth and directly related to the concentration and duration of oxygen treatment. The risk of retinopathy of prematurity rises dramatically from less than 10% at 26 weeks to above 50% in infants born at 24 weeks. About 3% of infants born before 28 weeks' gestation will require a hearing aid and 50% will be found to have learning difficulties at school requiring additional educational support. Preterm birth is associated with an increased prevalence of other medical disabilities, learning difficulties, and behavioral and psychological problems even in those without cerebral palsy. The risks of autism and mental retardation are increased 10-fold in preterm infants born before 28 weeks, and that of schizophrenia is increased fivefold. Difficulty with cognitive processes contributes to an increased risk of school problems in children born preterm. Only half of children born before 28 weeks are able to enter preschool with their peer group. The proportion of children born preterm who experience academic difficulties increases with age as the complexity of the schoolwork increases. Even in adults born preterm and who have no apparent medical problems, there are lower rates of high-level education and higher rates of low income and dependence on social security benefits. Mothers of infants born preterm are at increased risk of experiencing depressive symptoms. The length of time that the newborn preterm infant must stay in the hospital also affects the ability of the mother to fulfil her role in the family. Families caring for a child born preterm face long-term and multiple challenges. The impact on families is long term, with parents, siblings, finances and family functioning all affected. Families will need to continue to manage the effects of prematurity when the children are toddlers, reach school age, become adolescents and, in some cases, into adulthood. The parent's marital relationship is likely to become stressed, often leading to divorce and consequent worsening of parenting difficulties. Parents will experience higher stress levels through difficulties in supervision of the child, the child's peer relationships and self-esteem, the impact of the child's difficulties on family routines, and worrying about the child's future. Siblings are affected because of the decreased attention that they receive from their parents. The family as a unit is affected by the greater likelihood of not having additional children, the financial burden, limits on family social life, high levels of family stress and dysfunction, and parents' difficulty in maintaining employment.

Endocrinology and biochemistry of labor

To effectively predict and prevent labor requires a good understanding of the endocrinology and biochemistry underlying the onset of labor in humans, both at term and preterm (Fig. 28.4). Our understanding of the mechanisms leading to the onset of labor in the human remains incomplete, in part because the mechanisms of the onset of parturition in different species appear to have evolved differently, making the direct extrapolation of data from animal models to the human not necessarily valid.



Labor as an inflammatory process

Throughout pregnancy the uterine cervix needs to remain firm and closed whilst the body of the uterus grows by hypertrophy and hyperplasia but without significant fundal dominant contractions. For labor to be successful the cervix needs to be converted into a soft and pliable structure that can efface and dilate and the uterus needs to become a powerful contractile organ. There is no single endocrine or biochemical switch in the human that changes the uterus from its not-in-labor state to its in-labor state. The onset of labor is a gradual process which begins several weeks before delivery itself with changes in the lower pole of the uterus which cause cervical ripening and effacement. The onset of clinically identifiable contractions is a relatively late event in this process. Cervical ripening occurs through breakdown of collagen, changes in proteoglycan concentrations and an increase in water content. The lower segment of the uterus also stretches and relaxes and behaves physiologically more like the cervix than like the contractile upper segment of the uterus. These changes in the lower segment of the uterus are associated with an increase in the production of inflammatory cytokines, particularly interleukin (IL)-8 and prostaglandins from the overlying fetal membranes and decidua and from the cervix itself. Cervical ripening is associated with an influx of inflammatory cells into the cervix which release matrix metalloproteins that contribute to the anatomical changes associated with ripening. The later increase in finally dominant contractility in the upper segment of the uterus is associated with an increase in the expression of receptors for oxytocin and prostaglandins, in gap junction proteins, which mediate electrical connectivity between myocytes, and in more complex changes in the intracellular signaling pathways which increase the contractility of the myocytes.

Roles of progesterone, corticotrophin-releasing hormone and oxytocin

In many species progesterone is thought to play an important role in suppressing the onset of labor. Progesterone has a generally anti-inflammatory action within the uterus. As discussed above, many of the biochemical events associated with cervical ripening and the onset of labor are similar to those seen at sites of inflammation. In most species the onset of labor is heralded by withdrawal of progesterone. So, for example, in the rodent, prostaglandin-mediated regression of the corpus luteum leads to a fall in progesterone concentrations immediately prior to the onset of labor. In the sheep increased production of cortisol from the fetal adrenal signals fetal maturation and induces placental 17α-hydroxylase, which increases synthesis of estrogen at the expense of progesterone, again leading to progesterone withdrawal immediately prior to the onset of labor. There is no systemic withdrawal of progesterone in the human prior to the onset of labor, although there is an increase in the expression of genes formerly repressed by progesterone, which has led to the hypothesis of a 'functional progesterone withdrawal' mediated by changes in the expression or function of progesterone receptors or of cofactors needed for the function of the progesterone receptor. Another hypothesis is that inflammatory events seen within the uterus at the time of labor are associated with increased activity of the transcription factors nuclear factor (NF)-κB and AP-1 (transcription factors strongly associated with inflammation in other contexts such as asthma, inflammatory bowel disease or arthritis). NF-κB and AP-1 repress the function of the progesterone receptor and so could mediate functional progesterone withdrawal. Although in the mouse progesterone concentrations fall due to luteolysis just prior to labour, there is still sufficient circulating progesterone concentrations to activate progesterone receptors. In the mouse it appears that the final event leading to parturition is the increased production of surfactant protein A from the fetal lung, which stimulates the activity of NF-κB within the uterus leading to an influx of inflammatory cells, an increase in inflammatory cytokine synthesis and depression of the residual function of the progesterone receptor. It is an attractive hypothesis that pulmonary maturation in the human may signal the final phase of the onset of labor but there is at present no direct evidence that this mechanism applies in the human.

Circulating levels of corticotrophin-releasing hormone (CRH), synthesized in the placenta, increase progressively throughout pregnancy and especially during the weeks prior to the onset of labor. CRH-binding protein concentrations fall with advancing gestational age such that, approximately 3 weeks prior to the onset of labor, the concentration of CRH exceeds that of its binding protein. Unlike in the hypothalamus, placental CRH is upregulated by cortisol. Several studies have linked placental production of CRH with the timing of birth and have demonstrated that a premature rise in CRH is associated with preterm delivery. The upregulation of CRH by cortisol suggests a mechanism by which the fetus, through increased adrenal cortisol production, may signal its maturation and control the timing of birth. For much of pregnancy the CRH receptor expressed by the myometrium is linked to second messenger systems that promote relaxation. Near to term, however, CRH may enhance the contractile response to oxytocin and may stimulate the production of prostaglandins from the fetal membranes and the placenta. In the monkey, uterine

contractions occur only at night. In the days preceding labor and delivery there are nocturnal non-fundal dominant contractions which have been termed ‘contractures. The conversion from contractures to contractions is mediated by an increase in the production of oxytocin from the maternal posterior pituitary gland. In the monkey, therefore, while the fetus might signal its general readiness to be born through increased cortisol production from the adrenal, the precise timing of birth is signaled by the mother. This may be a mechanism of defense against predators which ensures that delivery is always at night. Contrary to the experience of many obstetricians, this phenomenon does not apply to the human. There is no increase in the production of oxytocin associated with the onset or progression of either preterm or term labor. There is, however, an increase in the expression of oxytocin receptors within the uterus and there is local production of oxytocin in the uterus, decidua and fetal membranes. Although oxytocin probably does not play an important role in the precise timing of parturition in the human, increases in the density of oxytocin receptors suggests that oxytocin does play a role in mediating contractility. Recent studies have shown that oxytocin acts not only to stimulate the uterus to contract, but also to upregulate inflammatory mediators within the uterus, therefore adding an additional ‘pre-labor’ mechanism of action for the hormone. Oxytocin also plays important postnatal functions in mediating the milk-let down reflex, contracting the uterus to prevent postpartum hemorrhage and having a effect on maternal bonding with the baby.

Causes of preterm labor

Preterm labor is not a single disease entity but is a syndrome that may have one or more causes. Research into the prediction and prevention of preterm labor has to some extent been made more difficult because many investigators have treated the syndrome as if it is a single disease. With the exception of studies specifically in multiple pregnancy and in populations of women with a short cervix, most clinical studies of interventions to prevent or delay preterm labor have not attempted to differentiate subjects on the basis of the underlying cause. Similarly, many studies which have attempted to identify biomarkers for preterm labor have not taken into account its multiple etiology. Preterm labor has been linked to cervical incompetence, abnormalities of haemostasias, infection within the uterus, placental abruption or decidual hemorrhage, fetal or maternal stress and multiple pregnancy. These various factors may act together to increase the likelihood of preterm delivery or to affect the gestational age at which preterm delivery occurs. Multiple pregnancy probably leads to preterm delivery through at least three mechanisms. Over-distension of the uterus leads to premature upregulation of contraction- associated proteins and of factors which mediate cervical ripening, all of which have been shown to be sensitive to mechanical stretch. Multiple pregnancy is associated with multiple placentas and therefore with an earlier rise in placental CRH concentrations in the circulation. The development of multiple corpora lutea may lead to increased production of relaxing and to premature cervical ripening. The incidence of multiple pregnancy has increased due to the trend of delayed childbirth, since multiple births occur with a greater frequency amongst older mothers. However, the principal contributing factor has been the linked increase in the use of assisted reproductive

technologies. This has been controlled to some extent in the UK by restricting the number of embryos transferred at *in vitro* fertilization, although poorly controlled ovulation induction therapies may continue to contribute to the problem.

Cervical function

With improved survival at early gestational ages, there is now overlap between second- trimester pregnancy loss and early preterm delivery. Historically, cervical incompetence was diagnosed in women who experienced persistent, often rapid and painless, late second- trimester pregnancy loss. More recently, the concept of cervical competence as a continuum has evolved. It is probable that cervical length and strength, together with the quality of the cervical mucus, contribute towards cervical function, both to retain the pregnancy within the uterus and to exclude potential bacterial pathogens from ascending from the vagina. Numerous studies have demonstrated a strong relationship between cervical length and the risk of preterm delivery. The cervix may be damaged (or completely removed) by surgery in the treatment of cervical cancer or, rarely, during a difficult instrumental vaginal delivery, or caesarean section at full dilatation. Historically, there were associations between diethylstilbestrol exposure *in utero* and developmental anomalies in the genital tract and cervical weakness. This ceased to be a problem in modern obstetric practice since the cohort of women exposed to the drug in the 1960s are now beyond reproductive age. A short or partially dilated cervix may allow bacteria to ascend into the lower pole of the uterus where, acting through the Toll-like receptors of the innate immune system which recognize bacterial components, they stimulate production of inflammatory cytokines, prostaglandins and the inflammatory response. This then leads to cervical ripening and shortening, which in turn decreases the ability of the cervix to act as either a mechanical or microbiological barrier and, ultimately, leads to the development of either localized or generalized chorioamnionitis and to preterm delivery. A short or weak cervix may therefore contribute to preterm delivery not only by leading to simple second-trimester miscarriage but also by contributing to a risk of ascending infection leading to a more classical spontaneous preterm labor. Delivery by caesarean section at or close to full dilatation of the cervix is now recognized as a risk factor for preterm birth. The probability is that difficult delivery leads to mechanical damage to the cervix, through the trauma from failed instrumental delivery, through a uterine incision made within cervical rather than lower segment tissue, or through damage to the cervix caused by the need to disimpact a deeply engaged fetal head. There is an association between risk of preterm delivery and cervical intraepithelial neoplasia (CIN). The greatest risk is in those women with CIN who have had a particularly deep large loop excision of the transformation zone (LLETZ) or a cold knife cone biopsy. In women who have had a deep LLETZ or a cold knife cone biopsy, mechanical damage to the integrity of the cervix is probably a major aetiological factor in their risk of preterm labour. However, there is a smaller underlying risk associated with CIN alone. It may be that human papillomavirus (HPV) infection is an independent risk factor for preterm birth. It is also possible that the underlying factors associated with the development of CIN following HPV infection in an individual woman may also be factors which increase her risk of preterm birth.

Genital tract infection

There is a strong correlation between infection within the uterus and the onset of spontaneous preterm labor. As discussed, activation of inflammatory mediators is a central part of the normal biology of parturition. Therefore, infection within the uterus has the potential to activate all the biochemical pathways, ultimately leading to cervical ripening and uterine contractions. It has been estimated that approximately 40% of all preterm births are associated with bacterial infection. The most likely source of infection is bacteria ascending from the vagina through the cervix into the lower part of the uterus. However, bacteria may also gain access to the amniotic cavity through hematogenous spread or by introduction at the time of invasive procedures. Following preterm delivery histological chorioamnionitis is usually more common and severe at the site of membrane rupture than elsewhere, such as overlying the placenta or umbilical cord. In virtually all cases of congenital pneumonia, inflammation of the fetal membranes is also present. Bacteria identified in the majority of cases of congenital infection are often also found in the maternal lower genital tract and, following twin preterm delivery, chorioamnionitis is more common and severe in the presenting twin than in the second twin (although this is not always the case). These factors all suggest that ascending infection from the lower genital tract is the commonest mechanism for chorioamnionitis. The most common microbes isolated from the amniotic cavity of women in preterm labor are *Ureaplasma urealyticum*, *Fusobacterium* and *Mycoplasma hominis*. More than 50% of patients in preterm labor will have more than one microorganism isolated from the amniotic cavity. Microorganisms can be identified in the fetal membranes of the majority of women delivering both preterm and at term. It is probable that some cases of spontaneous preterm delivery are due to an excessive inflammatory response to a lesser degree of bacterial invasion of the amniotic cavity. So, for example, bacterial vaginosis (see below) may be a greater risk factor for preterm labor in women who carry a high secretory form of the tumors necrosis factor (TNF)-α gene. There is now considerable interest in the role of the microbial communities in the vagina in the etiology of preterm birth. The collective term for the range of bacterial species in the vagina is ‘vaginal microbiota’. The collective term for all the bacterial genes present is ‘vaginal microbiome’ (although the term ‘microbiome’ is often used interchangeably with ‘microbiota’ to define a microbial community occupying a reasonably welldefined habitat which has distinct physicochemical properties). The study of the bacterial genes present in the vaginal microbiome is described as metagenomics. In reproductive life the vaginal microbiota is usually dominated by the presence of lactobacilli, representing more than 90% of bacterial species present. Lactobacilli secrete lactic acid, which maintains a low pH hostile to other microorganisms and which has anti- inflammatory actions. Lactobacilli also excrete specific antimicrobial proteins. A minority of women will have a *Lactobacillus*-depleted vaginal microbiota, and this may allow overgrowth of bacterial vaginosis (BV)-associated anaerobic organisms such as *Gardnerella vaginalis*, which creates a biofilm that allows other opportunistic bacteria to thrive. The increased estrogen concentrations of pregnancy increase the availability of vaginal mucosal glycogen, a source of energy for lactobacilli. Therefore, in general,

the proportion of lactobacilli increases in the vagina during pregnancy. The relationship between the structure of the vaginal microbiota and the risk of preterm birth varies from population to population. In some but not all populations in the USA, where *Lactobacillus* depletion is common, a dysbiosis *Lactobacillus*-depleted BV-like vaginal microbiota is a risk factor for preterm birth. In the UK, prevalence of a dysbiosis vaginal microbiota in pregnancy is low but is probably still a risk factor. However, the dominance of one particular species, *Lactobacillus iners*, appears to be a risk factor for both cervical shortening and preterm birth. *Lactobacillus inners* has less ability to excrete anti-inflammatory isomers of lactic acid or antimicrobial proteins, and may represent a transitional organism between healthy vaginal microbiota and vaginal dysbiosis or bacterial vaginosis.

Hemorrhage

Placental abruption may lead to the onset of preterm labor. This is thought to be through release of thrombin, which stimulates myometrial contractions by protease-activated receptors but independently of prostaglandin synthesis. This may explain the clinical impression that preterm labor associated with chorioamnionitis is often rapid whereas that associated with placental abruption is less so because there is no pre-ripening of the uterine cervix. Generation of thrombin may also play a role in preterm labor associated with chorioamnionitis when it is released as a consequence of decidual hemorrhage.

Fetal and maternal stress

There is evidence that both fetal and maternal stress may be risk factors for preterm labor. Fetal stress may arise in association with abnormal placentation and growth restriction. Maternal stress could be due to environmental factors. In both cases it is postulated that over- secretion of cortisol leads to upregulation of CRH production in the placenta.

Prediction of preterm labor

In the majority of cases of preterm labor obstetric management consists principally of attempting to suppress contractions in women who are already in established labor. As discussed in more detail later, this strategy is essentially ineffective. Obstetric strategies to reduce perinatal morbidity and mortality associated with preterm labor should ideally involve the early identification of women at risk and the use of prophylactic therapies. Prediction of preterm labor can be considered in two broad scenarios. Firstly, there is prediction at a time removed from the labor event itself, intended to direct possible prophylactic therapy. Secondly, there is the prediction of delivery in women who are symptomatic, essentially intended to differentiate those who are genuinely in preterm labor from those who have preterm contractions but are not at risk of imminent delivery. Attempts have been made to devise risk scoring systems based on socio-demographic characteristics, anthropomorphic characteristics, past history, patient behaviour and habits and factors in the current pregnancy. None of these systems has been found to have positive predictive values or sensitivities which make them clinically useful in identification of individual women at risk. Most systems rely heavily on past obstetric history and are therefore irrelevant to women having their first baby. At present there are no screening tests which are routinely applied to

primigravid women, or to multigravida women who are not at high risk for preterm labor. Women at high risk of preterm labor will initially be detected based solely on past obstetric history. Having had a single previous preterm delivery increases the risk of preterm delivery in a subsequent pregnancy four times when compared to a woman whose previous delivery was at term. A past obstetric history which consists of a term delivery followed by a preterm delivery confers a higher risk of preterm delivery in the third pregnancy than a past obstetric history that consists of a preterm delivery followed by a term delivery. This may be because the latter group contains a disproportionate number women whose preterm delivery was for 'non-recurring' causes such as placental abruption, whereas in the former group the preterm delivery following the term delivery may be due to damage to the cervix during the original term delivery.

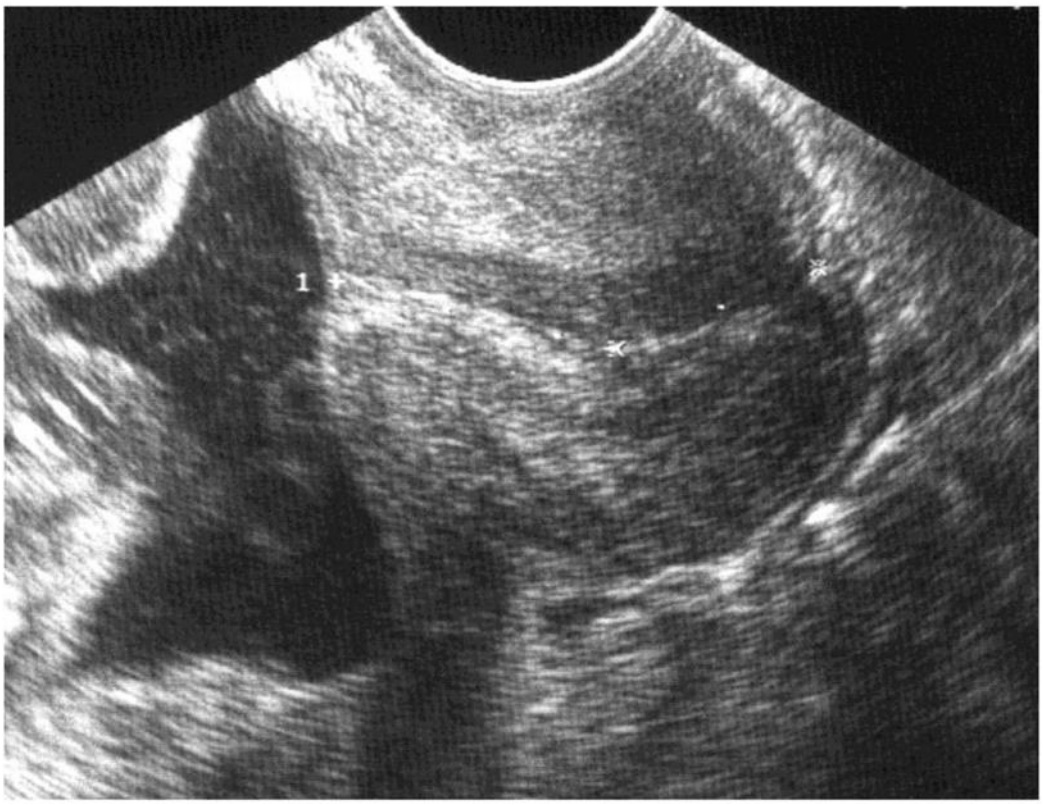
Ultrasound measurement of cervical length

There is very good evidence that transvaginal sonographic measurement of cervical length can be used to identify women at risk of preterm labor in both low- and high-risk pregnancies and in women who are symptomatic (Fig. 28.5). Transabdominal measurement of cervical length is unreliable because of the need for a full bladder, which may compress the cervix leading to an overestimate of its length, and because it is more difficult to obtain adequate views of the cervix with this technique. Transvaginal ultrasound should be performed with the bladder empty. The probe is placed in the anterior fornix of the vagina without undue pressure on the cervix and optimally the internal and external us and the echogenic endocervical mucosa should be identified along the length of the canal. For identification of risk in asymptomatic women (those who do not have symptoms of labor) two broad strategies are currently in common use: a single measurement in the mid-second trimester, or serial measurement of cervical length throughout the second and early third trimester of pregnancy.

A single measurement of cervical length, usually at the time of a routine ultrasound scan between 18 and 22 weeks, has been widely used to identify subjects at high risk of preterm birth for inclusion into intervention trials. If a screening strategy using a single ultrasound measurement of cervical length is used, then assessment between 21 and 24 weeks of gestation appears to be better than assessment prior to 20 weeks' gestation in predicting the risk of preterm labor. However, this is to a certain extent a self-fulfilling prophesy since clearly the closer to the actual onset of preterm labor the assessment of cervical length is made, the more likely it is that the cervix will be found to be short. It is arguable that identification of a risk of preterm labor as late as 23 weeks may be too late for any potential prophylactic therapies to be fully effective. In addition, such a strategy is unable to detect any of the women whose pregnancy loss or preterm delivery occurs prior to 23 weeks. A large number of studies have examined the relationship between gestational age, cervical length and the risk of preterm delivery (Fig. 28.6). Many studies have used single cut-off values. So, for example, a cervical length of 15 mm or less at 20–24 weeks predicts a risk of preterm delivery prior to 34 weeks' gestation of approximately 50% in a low-risk population. It is absolute cervical length rather than the presence or absence of funneling which is the principal predictor of spontaneous preterm birth (although

clearly the presence of funneling will lead to a shorter cervical length). It has been suggested that the introduction of routine measurement of cervical length at the time of the second-trimester anomaly ultrasound scan would enable screening of low-risk populations. This concept is greatly predicated on the assumption that an effective intervention is available (see section on progesterone and cervical cerclage). The value of routine measurement of cervical length also depends on the prevalence of a short cervix and the incidence of preterm birth in the background population. In UK populations this approach will only detect about 15% of all preterm births, a reflection of the multi-etiological nature of the syndrome. Women at high risk of preterm birth may be offered serial measurement of cervical length to assess their risk of preterm labor. This approach appears to be superior to a single measurement in assessing the risk of preterm delivery. It has been widely advocated as an approach for the detection of women who would benefit from progesterone prophylaxis during pregnancy. It is also a particularly useful approach in women with a history of a previous preterm birth or second-trimester pregnancy loss in whom a diagnosis of cervical insufficiency or incompetence is not clear and can be used to reduce the number of unnecessary cervical cerclage procedures performed. In this management strategy, cervical cerclage would be indicated either when cervical length reduces to a fixed cut-off, commonly 25 mm, or falls below the 10th or 3rd centile for cervical length at that gestational age. In continental Europe it is common practice to perform a vaginal assessment of cervical length at each antenatal consultation, although multicenter trials have shown that this policy is of no benefit in predicting the risk of preterm delivery.

(a)



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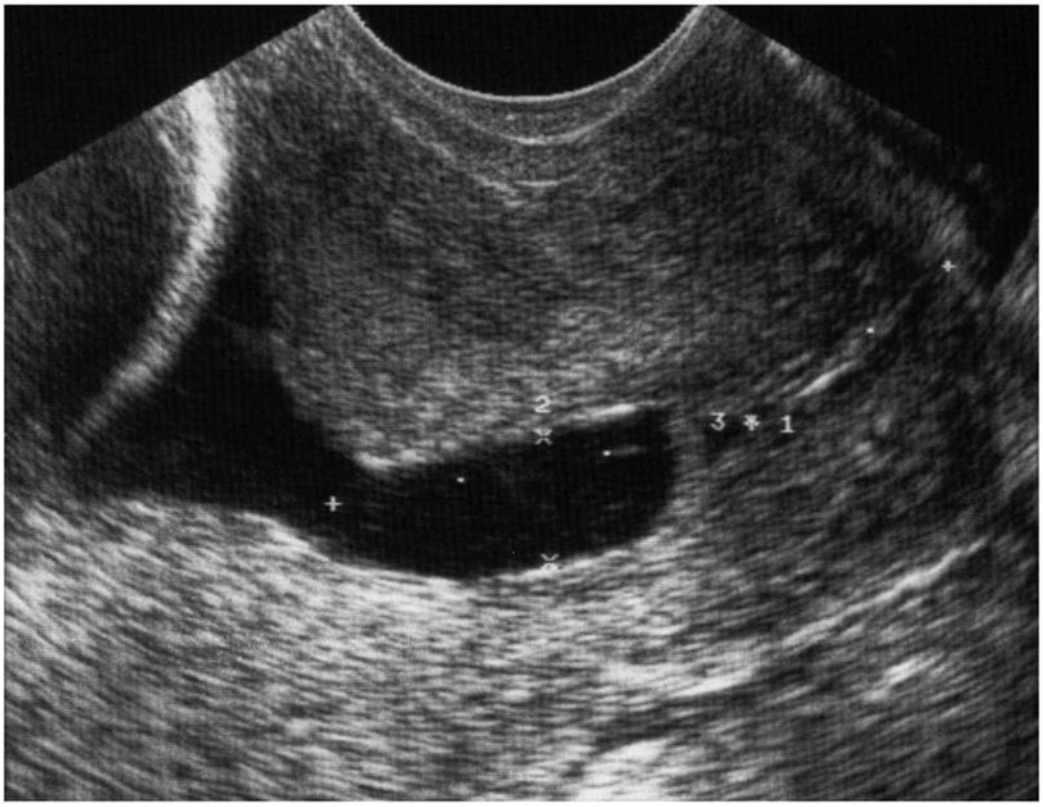
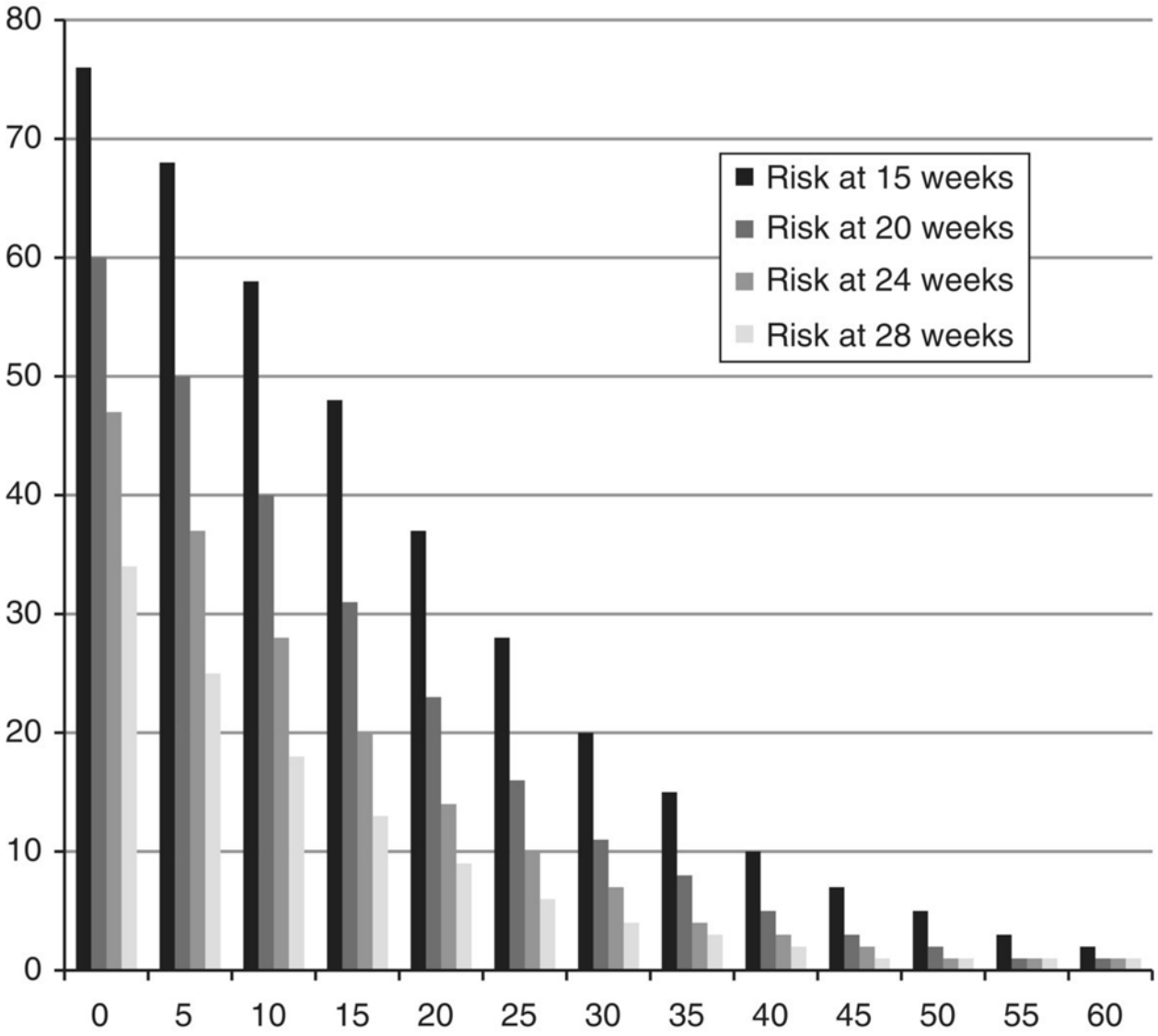




Bacterial vaginosis

As already discussed, BV is a risk factor for preterm birth, although most studies have shown that treating BV with antibiotics does not change the risk. Studies of the risk of preterm labor associated with BV have reported widely varying results. However, it seems that, overall, BV approximately doubles the risk of preterm delivery. It also appears that there is a relationship between the gestational age at diagnosis of BV and the risk of preterm delivery, in that if BV is diagnosed earlier in pregnancy this appears to be associated with a higher risk of preterm delivery. Routine screening for BV is not therefore undertaken in low-risk populations. Some obstetricians do include screening for BV in the management of high-risk populations, and this is currently undertaken by non-genetic techniques, although the future introduction of DNA sequence-based bacteriology may change this situation. Currently, diagnosis of BV can be made on Gram staining of vaginal fluid using either Nugent's or Spiegel's criteria, by gas–liquid chromatography of vaginal fluid (finding a high ratio of succinate to lactate) or on clinical grounds based on a high vaginal pH, a fishy odor in a thin homogeneous vaginal discharge and the presence of clue cells in the discharge on a wet mount. There is no significant difference in the ability of each of these diagnostic tests to predict preterm birth. Although there is reasonably good evidence that BV is a risk factor for preterm

delivery, it is less clear that treating it with antibiotics is beneficial. This may be in part because various studies of BV have used different antibiotics in different regimens and at different times, but it may also reflect the fact that antibiotics may not necessarily result in the re-establishment of normal bacterial flora. The two antibiotics commonly used in the treatment of BV are metronidazole administered orally or clindamycin, which may be given either orally or vaginally. Clindamycin may have advantages over metronidazole since it has better activity against anaerobic bacteria and *Mycoplasma hominis* and *Ureaplasma urealyticum* which are often associated with BV. While screening of pregnant women who are at high risk for preterm delivery based on their past obstetric history or other factors might be justified, there is currently no strong evidence to recommend the routine screening and treatment of the general obstetric population.

Fetal fibronectin

Fetal fibronectin is a glycoprotein variant of the fibronectin family present in amniotic fluid, placenta and the extracellular substance of the decidua. Its synthesis and release re increased by the mechanical and inflammatory events which occur prior to the onset of labor. Fibronectin is often described as 'leaking' from disruption to the fetal membranes and decidua in the lower pole of the uterus associated with the early biochemical events of parturition. However, it is also an inflammatory response gene, and therefore concentrations of fibronectin in vaginal fluid can be considered to also be a marker of inflammation (which may be pathological or a normal part of the onset of labor at term). Fetal fibronectin may normally be detected in vaginal secretions at levels in excess of 50 ng/mL up to 20 weeks' gestation and again after 36 weeks' gestation. Detection up to 20 weeks is possible because the amniochorion is not fully fused with the decidua until that time. Detection closer to term is a feature of the normal mechanical and biochemical events leading to normal term labor. The presence of fibronectin in vaginal secretions at levels above 50 ng/mL between 20 and 36 weeks is therefore not normal and may be used to predict a risk of preterm labor. When originally introduced as a commercial test, fibronectin analysis was principally intended to be used in women who present with preterm contractions to differentiate those with a risk of imminent delivery. However, it is now being increasingly used to predict risk in women who are asymptomatic but at risk for other reasons, in particular cervical shortening. The currently available bedside testing kits allow quantification of the concentration of fibronectin in the vaginal fluid, which has improved the predictive performance of the test. So, for example, women with a cervical length below 25 mm between 22 and 28 weeks, but with a fetal fibronectin concentration of less than 10 ng/mL, will have a risk of preterm birth before 34 weeks of less than 10%; this rises to over 50% if the fibronectin concentration is greater than 200 ng/ml. Predictive algorithms (e.g. QUIPP, Apple Store) have now become available that combine the information of past obstetric history, gestational age, cervical length and fibronectin concentration to produce an estimate of risk delivery within a defined time period (e.g. 7 days) or prior to a defined gestational age (e.g. 34 weeks). These algorithms have been developed based on populations who had interventions if they were identified as being at high risk and therefore their general applicability, particularly to low-risk

populations, is uncertain. Nevertheless, they act as a useful guide to enable clinicians to take into account all the risk factors for preterm birth and to direct therapy and counsel patients about the risks and benefits of interventions.

Prevention of preterm labor

In primigravid women with no other significant risk factors for preterm delivery there is currently no effective method for the prediction of preterm labor and therefore management can only be instituted at the time of acute presentation with contractions. However, it is possible to identify a group of women in the antenatal period who are at risk of preterm delivery based on their past obstetric history, the presence of abnormalities of the genital tract, and use of screening tests such as transvaginal ultrasonic measurement of cervical length and detection of fetal fibronectin in vaginal secretions. A continuing problem in the direction of therapies intended to reduce the risk of preterm birth is a lack of suitable tools to stratify women at risk into different etiological groups. Most studies of interventions have either had no classification or have selected subgroups of women, for example those with a multiple pregnancy or those with a short cervix. Even in those subgroups, however, the underlying etiology may be different. So, for example, it is possible that damage to the cervix caused by an excisional treatment for CIN, may result in both cervical incompetence and a physically shorter cervix. Such women may benefit from cervical cerclage. However, the cervix may have its structural integrity compromised without necessarily being rendered any shorter and would nevertheless still benefit from cerclage. Cervical shortening may be due to activation of inflammation within the vagina and cervix, in which case cerclage might be detrimental. It is possible that some of the dramatic differences in the effectiveness of interventions that are seen in different clinical trials may arise from enrolment of women whose underlying etiology of their risks of preterm birth are different, despite the apparent presentation, for example with a short cervix, being similar. At present, no prophylactic therapy has been demonstrated to be unequivocally beneficial in preventing the onset of preterm labour in a high-risk population. Commonly used therapies include cervical cerclage and progesterone. Previously, non-steroidal anti-inflammatory drugs and oral beta-sympathomimetics have been used. Vaginal pessaries are being studied.

Cervical cerclage

The objective of the MRC/RCOG multicenter randomized trial of cervical cerclage, published in 1993, was to assess whether cervical cerclage in women deemed to be at increased risk of cervical incompetence prolongs pregnancy and thereby improves fetal and neonatal outcome. However, women were randomized only if their obstetrician was uncertain whether to recommend cervical cerclage. Therefore, cervical cerclage was compared with a policy of withholding the operation unless it was considered to be clearly indicated. In this study, the largest ever conducted of this question, the overall preterm delivery rate was 28% and there were fewer deliveries before 33 weeks in the cerclage group (13% vs. 17%). This difference was reported to be reflected in deliveries characterized by features of cervical incompetence: painless cervical dilatation and pre-labor rupture of the membranes. The use of cervical cerclage was associated with a doubling of the risk

of puerperal pyrexia. Based largely on these data, current UK guidelines suggest that history-indicated cerclage should be offered to women with three or more previous preterm births and/or second- trimester losses. Various tests, including assessment of cervical resistance index, hysterography or insertion of cervical dilators, have been found to have no benefit in predicting cervical weakness. Never *the less* a clinical examination of the cervix of a woman considered at risk is beneficial. It will highlight any congenital or acquired abnormalities and will identify the women in whom cerclage may be a more challenging procedure than expected before discovery on the operating table. Many obstetricians currently use transvaginal ultrasound measurement of cervical length to assess risk of preterm birth and target intervention by cervical cerclage in women where there is uncertainty about the possible benefit. If ultrasound-indicated cervical cerclage is to be used, the appropriate threshold has not yet been universally agreed, although a length below 25 mm is a commonly used cut-off. The presence of visible fetal membranes at the time of cervical cerclage is a strong prognostic indicator for the risk of preterm delivery. Visible fetal membranes are never seen at a cervical length greater than 15 mm. An individual patient data meta-analysis of four large studies of targeted cervical cerclage in women with a short cervix taken from a general obstetric population with no increased background risk of preterm birth showed that cervical cerclage was not beneficial. It has therefore generally been concluded that cervical cerclage is of no benefit in a woman with a short cervix but no other risk factors for preterm labor. However, in the analysis the selected cut-off cervical length for cerclage varied between less than 15 mm and less than 25 mm, and the ultrasound examinations were performed relatively late in pregnancy at 22–24 weeks. The results of this meta-analysis also stand in stark contrast to a much smaller earlier study which showed a marked benefit of cervical cerclage undertaken by a single senior skilled obstetrician. As discussed later, there are various aspects of the technical performance of the operation that will affect the outcome. It is possible that the failure to demonstrate benefit of cervical cerclage in a large general population of women with short cervix is partly due to the short cervical length cut-off, late gestational age at screening, variable skill and experience of the operators and technique of the procedure. It is also probably the case that a population of women at risk of preterm birth with a short cervix at the end of the second trimester of pregnancy represents a mixture of women with genuine mechanical cervical problems, who would probably benefit from cervical cerclage, and women whose cervix is short for other reasons, who would probably not benefit and may even be harmed (see discussion on effects of suture material). Whilst the current evidence is that cervical cerclage is not beneficial in women whose only risk of preterm birth is a short cervix in the late second trimester, there is good evidence to study, the largest ever conducted of this question, the overall preterm delivery rate was 28% and there were fewer deliveries before 33 weeks in the cerclage group (13% vs. 17%). This difference was reported to be reflected in deliveries characterized by features of cervical incompetence: painless cervical dilatation and pre-labour rupture of the membranes. The use of cervical cerclage was associated with a doubling of the risk of puerperal pyrexia. Based largely on these data, current UK guidelines suggest that

history-indicated cerclage should be offered to women with three or more previous preterm births and/or second- trimester losses. Various tests, including assessment of cervical resistance index, hysterography or insertion of cervical dilators, have been found to have no benefit in predicting cervical weakness. Nevertheless, a clinical examination of the cervix of a woman considered at risk is beneficial. It will highlight any congenital or acquired abnormalities and will identify the women in whom cerclage may be a more challenging procedure than expected before discovery on the operating table. Many obstetricians currently use transvaginal ultrasound measurement of cervical length to assess risk of preterm birth and target intervention by cervical cerclage in women where there is uncertainty about the possible benefit. If ultrasound-indicated cervical cerclage is to be used, the appropriate threshold has not yet been universally agreed, although a length below 25 mm is a commonly used cut-off. The presence of visible fetal membranes at the time of cervical cerclage is a strong prognostic indicator for the risk of preterm delivery. Visible fetal membranes are never seen at a cervical length greater than 15 mm. An individual patient data meta-analysis of four large studies of targeted cervical cerclage in women with a short cervix taken from a general obstetric population with no increased background risk of preterm birth showed that cervical cerclage was not beneficial. It has therefore generally been concluded that cervical cerclage is of no benefit in a woman with a short cervix but no other risk factors for preterm labor. However, in the analysis the selected cut-off cervical length for cerclage varied between less than 15 mm and less than 25 mm, and the ultrasound examinations were performed relatively late in pregnancy at 22–24 weeks. The results of this meta-analysis also stand in stark contrast to a much smaller earlier study which showed a marked benefit of cervical cerclage undertaken by a single senior skilled obstetrician. As discussed later, there are various aspects of the technical performance of the operation that will affect the outcome. It is possible that the failure to demonstrate benefit of cervical cerclage in a large general population of women with short cervix is partly due to the short cervical length cut-off, late gestational age at screening, variable skill and experience of the operators and technique of the procedure. It is also probably the case that a population of women at risk of preterm birth with a short cervix at the end of the second trimester of pregnancy represents a mixture of women with genuine mechanical cervical problems, who would probably benefit from cervical cerclage, and women whose cervix is short for other reasons, who would probably not benefit and may even be harmed (see discussion on effects of suture material). Whilst the current evidence is that cervical cerclage is not beneficial in women whose only risk of preterm birth is a short cervix in the late second trimester, there is good evidence to Similarly, cerclage does not appear to be of benefit in women with multiple pregnancy and a short cervix but no other risk factors for preterm birth. This underlines the etiological differences in the risk of preterm birth between singleton and multiple pregnancy. There are no large studies of the role of cerclage in women with twins who have a past history of second-trimester pregnancy loss or preterm delivery. However, it would be illogical to deny a woman who had previously benefited from cervical cerclage, a cerclage in a subsequent pregnancy because she was carrying twins.

Emergency 'rescue' cerclage

Rescue cervical cerclage may be performed when a woman is admitted with silent cervical dilatation and bulging of the membranes into the vagina but without the onset of uterine contractions. Characteristically, such women present with slight vaginal bleeding, a watery vaginal discharge, or vague pelvic or vaginal pain. The available literature, mostly composed of case reports and small case series, suggests that rescue cerclage may delay delivery by a further 5–7 weeks on average compared with expectant management/bed rest alone, associated with a twofold reduction in the risk of delivery before 34 weeks. However, there are concerns that emergency or rescue cerclage might convert a second-trimester pregnancy loss into an early preterm delivery with its associated handicap risk, particularly in the context of chorioamnionitis. Adverse features which should contraindicate rescue cervical cerclage include evidence of chorioamnionitis: maternal pyrexia, abdominal pain, contractions, raised white blood cell count or C reactive protein levels. Whether antibiotics are beneficial in such cases has not been established.

Non-steroidal anti-inflammatory drugs

The central role for prostaglandins and inflammatory cytokines in the onset of labor at term and in the etiology of preterm labor suggests that non-steroidal anti-inflammatory drugs (NSAIDs) may be beneficial in preventing preterm delivery. NSAIDs work largely by inhibition of the cyclooxygenase enzymes which catalase the synthesis of prostaglandins. However, various NSAIDs also have other mechanisms of action, including effects on intracellular signaling pathways and on inflammatory transcription factors such as NF-κB and AP-1. Whilst there are several studies of the use of NSAIDs in the acute management of preterm labor, there are few good randomized trials of their use as prophylaxis. NSAIDs are associated with significant fetal side effects, in particular oligohydramnios and constriction of the ductus arteriosus. Oligohydramnios occurs in up to 30% of fetuses exposed to indomethacin. The effect is dose dependent and may occur with both short-term and long-term exposure. Discontinuation of therapy usually results in a rapid return of normal fetal urine output and resolution of the oligohydramnios. Constriction of the ductus arteriosus occurs in up to 50% of fetuses exposed to indomethacin at gestational ages greater than 32 weeks. There is a relationship between dose and duration of therapy and gestational age. Ductal constriction is seen less commonly below 32 weeks and rarely below 28 weeks. Long-term indomethacin therapy, particularly after 32 weeks, is therefore associated with a significant risk of persistent pulmonary hypertension. More detailed ultrasound studies have shown that administration of indomethacin is associated with a rapid reduction in hourly fetal urine production but that oligohydramnios may develop more slowly and become significant at between 15 and 28 days. There are two major isoforms of the cyclooxygenase enzyme, COX1 and COX2. COX1 is constitutively expressed in the majority of cells whereas COX2 is inducible and catalyses' the synthesis of prostaglandins at the sites of inflammation. Since it is probable that it is COX1 whose function is important for fetal renal function and ductal patency, it was hoped that the use of NSAIDs selective or specific for COX2 might be associated with a lower risk of fetal side effects. However, nimesulide, which is approximately 100-

fold more effective in inhibition of COX2 than COX1, is associated with an incidence of fetal oligohydramnios similar to that seen in fetuses exposed to indomethacin and there have been isolated case reports of fatal fetal renal failure. Prophylactic use of the COX2-specific rofecoxib, although associated with weaker effects on both fetal renal function and the ductus arteriosus than indomethacin or nimesulide, is associated with an increased rate of preterm delivery. The reasons for this are unclear but probably represent an effect on anti-inflammatory as well as proinflammatory prostaglandins. At present therefore there is no good evidence that NSAIDs confer benefit when used as prophylaxis for preterm labor. They are associated with a significant risk of potentially life- threatening side effects. If NSAIDs such as indomethacin are to be used, perhaps as short-term therapies in association with cervical cerclage, and particularly for more than a few days after 28 weeks, then it is essential that there should be ultrasound surveillance of fetal urine production or amniotic fluid index and of the ductus arteriosus and that therapy should be stopped when fetal side effects become evident.

Progesterone

Progesterone is probably the most widely used intervention to prevent preterm labor worldwide. Currently, two different progestin preparations are in common use. The synthetic 17α-hydroxyprogesterone caproate, which is chemically similar to testosterone and is not a natural progesterone metabolite, has been shown to reduce the risk of preterm birth in women at high risk based on past history but who do not have a short cervix. Current evidence suggests that 17α-hydroxyprogesterone caproate is not effective in the group of women whose risk of preterm birth is predicted by a short cervix, nor is it effective in women at risk of preterm birth because of multiple pregnancy. The mechanism of action of 17α-hydroxyprogesterone caproate is unclear. Concentrations of progesterone in the circulation during normal pregnancy are substantially above the K_d for the progesterone receptor. As discussed, unlike in other species, in the human progesterone concentrations in the circulation do not fall at the time of either term or preterm labor. There is no evidence for lower progesterone concentrations either in the circulation or in tissues in women at risk of preterm birth. The relative binding affinity of 17α-hydroxyprogesterone caproate for nuclear progesterone receptors is only about 30% that of natural progesterone. 17α-hydroxyprogesterone caproate does not inhibit myometrial contractions *in vitro*. Several large randomized trials in multiple gestations have identified harm related to exposure to 17α-hydroxyprogesterone caproate, and the synthetic drug is therefore contraindicated in this population. In addition, 17α-hydroxyprogesterone caproate is given as a weekly intramuscular injection, which itself is very painful and therefore patient compliance may not be good. For these reasons 17α-hydroxyprogesterone caproate has not found great popularity outside the USA. Probably the most widely used progesterone for prevention of preterm birth is natural progesterone administered as a vaginal pessary. Vaginal progesterone appears to be principally effective in patients identified as at risk of preterm labor because of a short cervix. It is not effective in women at risk who have a normal cervical length, nor has it been proven to be of benefit in multiple pregnancy, although there is some evidence that it may be

beneficial in women with twins who also have a short cervix. Unlike 17α-hydroxyprogesterone caproate, natural progesterone has not been associated with any harm to either mother or fetus. Both an individual patient data meta-analysis of five randomized controlled trials and a systematic review of 36 randomized controlled trials support the use of vaginal progesterone to reduce preterm birth in women with singleton pregnancies at risk of preterm birth associated with a short cervix. The results of both systematic reviews are mainly driven by the 2011 international PREGNANT trial, a randomized controlled trial in which pregnant women at low risk for preterm birth were screened for cervical length with transvaginal ultrasound and progesterone given if the cervix measured 10–20 mm. Overall, the study showed a clear benefit for progesterone in reducing risk of preterm birth in this group, although the trial also showed substantial heterogeneity across study sites. Progesterone appeared to be highly effective in several studies outside the USA, but to have no significant effect on preterm birth rates in US populations. Vaginal progesterone was declined FDA approval for use in the USA partly because of a lack of significant effect on preterm birth rates in the US study centers. The largest randomized controlled trial of vaginal progesterone, OPPTIMUM, was undertaken in the UK and published in 2016. This included women at risk of preterm birth for a variety of reasons and was powered to include three primary outcomes: preterm birth, a composite of neonatal death or severe morbidity, or childhood neurodevelopment. It showed that vaginal progesterone did not reduce any of the primary outcomes but that there was no harm associated with progesterone use. The study did show a non-statistically significant reduction in the risk of preterm birth in women randomized to progesterone because of a short cervix and has been criticized because of a lower compliance rate than seen in other studies, and because the study was not powered to specifically study the patient with a short cervix. A meta-analysis performed after publication of OPPTIMUM continues to show a significant benefit of vaginal progesterone in women with a short cervix. The potential mechanism of action of natural progesterone is also unclear. The concentrations of progesterone in the circulation during normal pregnancy are substantially above the K_{d} for the nuclear progesterone receptor. There is no evidence for lower progesterone concentrations in the circulation of women at risk of preterm birth, and administration of vaginal progesterone to women at risk does not elevate circulating progesterone concentrations. It seems likely that the mechanism of action of natural progesterone is local rather than systemic, and it is possible that it may act both through the parent hormone and through metabolites. Progesterone may act to increase the volume and quality of cervical mucus, hence improving physical and biochemical barriers to ascending infection. One widely is excepted hypothesis is that progesterone may act as an anti-inflammatory. In cell culture model studies, progesterone inhibits cytokine- or lipopolysaccharide-stimulated activation of inflammatory transcription factors, prostaglandin synthetic enzymes, and the synthesis of prostaglandins and cytokines. However, clinical studies have shown that progesterone does not inhibit cervical–vaginal inflammatory mediators, nor does it have any effect on the vaginal microbiota. outcome. A pool of amniotic fluid greater than 2 cm is associated with a low incidence of pulmonary hypoplasia. Although

many women with preterm rupture of the fetal membranes go into labor fairly quickly thereafter, those women who do not establish in preterm labor shortly after PPROM are at risk of chorioamnionitis. This may represent infection ascending into the uterine cavity, although in some cases PPROM may follow established chorioamnionitis. In either case such infection can be harmful and potentially fatal to both mother and baby and so PPROM requires careful clinical monitoring to allow early detection and treatment of *in utero* infection and chorioamnionitis. Accurate diagnosis of PPROM is therefore important. This may be based on history, identification of a pool of liquor in the vagina and of oligohydramnios on ultrasound. Biochemical tests of PPROM are available that depend on detection of nitrazine (pH), placental α-microglobulin (PAMG)-1 or insulin-like growth factor binding protein (IGFBP)- 1 in vaginal fluid. Nitrazine (pH) testing does not appear to be useful in diagnosis of PPROM, having a clinically useless positive predictive value. Tests for PAMG-1 or IGFBP-1 have clinically useful positive predictive values and so could be used where clinical assessment of PPROM is equivocal but if clear pooling of amniotic fluid is seen are probably unnecessary. Once PPROM has been confirmed the management is a balance between the risks of prematurity if delivery is encouraged versus the risks of maternal and fetal infection if there is conservative management. It is important to recognize, especially in the context of PPROM, that increasing gestational age at delivery by increasing the latency period is not necessarily associated with improvements in neonatal and childhood outcomes. The links between chorioamnionitis, and particularly funicity, and lung disease and cerebral palsy imply that to deliberately retain the fetus in an adverse uterine environment could potentially worsen early neonatal outcomes and thus the risk of cerebral palsy. The ORACLE II study from 2001 showed that prophylactic use of erythromycin improves neonatal morbidity, reduces the risk of sepsis and is associated with a longer latency period, whereas co-amoxiclav increases the risk of necrotizing enterocolitis and should therefore be avoided. Antibiotics of any type, given prophylactically, do not reduce the incidence of perinatal death or neonatal encephalopathy and do not affect the rates of maternal sepsis or maternal death. These findings have been confirmed by meta-analysis of subsequent studies. Follow-up of the babies in the ORACLE I study showed no differences in serious childhood morbidity at 7 years, and in particular no differences in cerebral palsy rates between babies whose mothers were or were not given antibiotics following PPROM. Erythromycin has a number of potential advantages over other antibiotics in PPROM. It can be administered orally and is effective against group B *Streptococcus*, other streptococcal and staphylococcal infections and *Mycoplasma*, all of which may be implicated in chorioamnionitis. Its use is therefore currently recommended in the UK as prophylaxis for up to 10 days following a diagnosis of PPROM. However, this is not based on any stratification of the causes of PPROM. Recent studies have demonstrated that there is a more complex relationship between the vaginal microbiota, PPROM and erythromycin. In cases where the vaginal microbiota is largely *Lactobacillus* dominated, erythromycin may lead to the elimination of potentially protective *Lactobacillus* and allow a dysbiosis BV-like microbiota to become established. A dysbiosis vaginal microbiota correlates with

the development of chorioamnionitis and funicity and is therefore a risk factor for later neurodevelopmental problems. It is probable that the role of erythromycin will need to be re- evaluated when diagnostic tools to assess the vaginal microbiota within clinically useful time scales become available. Management of PPROM continues to be controversial. There is currently no consensus on how to manage women whose membranes rupture between 34 to 37weeks gestation. Most obstetricians will institute conservative management in uncomplicated PPROM before 34 weeks and many would induce labor relatively early in women whose membrane rupture occurs subsequent to 37 weeks. In any woman labor should be induced if there is good evidence of infection, although making a diagnosis of chorioamnionitis may be challenging (discussed below). A large randomized controlled trial from the Netherlands, PRROMEXIL (PPROM Expectant Management versus Induction of Labor) published in 2012 compared immediate induction of labor or expectant management in women with PPROM between 34 to 37 weeks of gestation. This found that the risk of chorioamnionitis was slightly reduced in the induction of labor group compared with the expectant management group but there were no differences in rates of neonatal sepsis, RDS or caesarean section. Because fewer babies than expected born to the women in the expectant management group developed neonatal sepsis, the trial was underpowered for this outcome; however, a subsequent meta-analysis of eight trials confirmed all these findings. In 2016, the PPROMT trial, a multicenter randomized controlled trial performed at 65 centers across 11 countries, showed that expectant management does not increase the risk of neonatal sepsis whilst early delivery was associated with increased risk of RDS. Mothers in the expectant management group were more likely to have evidence of sepsis at the time of delivery, but less likely to require caesarean section. From these studies it is reasonable to conclude that, in the absence of signs of infection or fetal compromise, a policy of expectant management with appropriate surveillance of maternal and fetal well-being should be followed in pregnant women who present with PPROM up to 37 weeks. It is probably the case that the later the PPROM, the lower should be the index of suspicion for chorioamnionitis leading to induction of labor. Lower genital tract swabs are routinely taken in women with PPROM. Positive cultures for potential pathogens do not correlate well with the risk, or development, of chorioamnionitis; however, they are useful in determining the causative organisms once chorioamnionitis develops and in directing antibiotic therapy for both the mother and the preterm neonate. Conservative management should include clinical surveillance for signs of chorioamnionitis, including regular recording of maternal temperature and maternal and fetal heart rate. The roles of white cell count (WCC) and C-reactive protein (CRP) are frequently misunderstood. Neither WCC or CRP are highly specific for chorioamnionitis. There is wide overlap, at the lower ends of the value ranges, between cases with and without histologically proven chorioamnionitis. Chorioamnionitis is often associated with a ‘normal’ WCC or CRP value. WCC may be normally elevated in pregnancy, will rise in response to antenatal corticosteroid therapy and has a relatively narrow range, rarely being less than 10×10^6/L and

rarely exceeding 20×10^6/L, whether there is chorioamnionitis or not. CRP is a better indicator of chorioamnionitis, but is not good for screening for the development of chorioamnionitis because of its low specificity at the cut-off values needed to give high sensitivity, and its inability to 'predict' chorioamnionitis (in other words CRP remains low until chorioamnionitis actually develops). Most studies have used CRP cut-off values of 5, 12 or 20 mg/L. Where low cut-off values are used the sensitivity improves (i.e.most true cases of chorioamnionitis are correctly identified) but this is at the expense of specificity (i.e. many women who test positive do not in fact have chorioamnionitis). As cut-off values are increased the number of false positives is reduced but at the expense of failing to identify many genuine cases of chorioamnionitis. When upper limits of CRP are set at 30, 35 or 40 mg/L, the last CRP before delivery is 90, 95 and 100% specific for chorioamnionitis. Therefore, whilst a low CRP value is not reassuring, a high value (>50 mg/mL) has a very high association with chorioamnionitis, particularly if it has risen rapidly. Chorioamnionitis should therefore be strongly suspected if there is clinical evidence (tenderness, pyrexia, maternal and/or fetal tachycardia), if there is a rapid rise in CRP values, or if a single CRP value is very high in the absence of any other clinical explanation such as pneumonia, pyelonephritis, deep vein thrombosis or pulmonary embolism. The absence of fetal movements or fetal breathing movements is also an adverse sign. The use of ultrasound measurement of cervical length in women with PPROM is uncertain. Some studies have shown that cervical length is predictive of latency, others have not. Ultrasound assessment is probably preferable to digital assessment since it appears to be associated with little risk of the introduction of infection. However, at present the technique is not generally used in the management of PPROM. The current evidence is that tocolytic therapy for women with preterm contractions following PPROM leads to an increase in maternal chorioamnionitis without significant benefits to the infant. The potential benefits of tocolytic drugs do not apply in the majority of cases of PPROM since there is usually time for administration of corticosteroids and *in utero* transfer before the onset of preterm labor itself. The dilemma about when to induce labour in cases of PPROM often does not materialize since 50% of women being managed conservatively will deliver within 7 days. The development of chorioamnionitis will stimulate the mechanisms leading to the onset of labor. Labor itself is therefore a marker of potential chorioamnionitis and so should not be inhibited.

Management of symptomatic preterm labor. Prediction of delivery risk in symptomatic preterm labor.

Of women who present to hospital with preterm contractions and are thought to be in threatened preterm labor, over 70% will remain pregnant for the following 14 days or more. As discussed in more detail later, there is little evidence to suggest that use of tocolytics, namely drugs intended to suppress uterine contractions, confer any significant benefit in cases of preterm labor. The improvement in neonatal morbidity and mortality seen with advancing gestational age is often used as an argument for the potential benefit of delaying preterm labor using tocolytic agents. However, there is no evidence that tocolytic drugs confer this benefit and there is a

real risk that to deliberately prolong a pregnancy, particularly in the context of chorioamnionitis, might lead to harm through retaining the fetus in an adverse intrauterine environment. There are clear benefits to the timely administration of magnesium sulfate ($MgSO_4$) and corticosteroids to reduce the risk of neonatal morbidity (see below), and to *in utero* transfer to a perinatal center with suitable neonatal intensive care facilities. Inappropriate administration of multiple courses of corticosteroids is associated with harm to the fetus, whilst unnecessary *in utero* transfer is expensive and blocks both obstetric beds and neonatology intensive care cot, to the detriment of other mothers and babies who might benefit from transfer. There is therefore a clear need for predictive tests that can determine which women who present with preterm contractions are genuinely at risk of delivery within the next 7 days and which are not. As with prediction in asymptomatic women, at present the two modalities in common use are transvaginal measurement of cervical length and fetal fibronectin concentrations in the vaginal fluid.

Ultrasound measurement of cervical length

The use of ultrasound measurement of cervical length in women symptomatic of threatened preterm labor varies geographically. In the USA almost all obstetric residents are skilled in ultrasound measurement of cervical length and suitable ultrasound machines are available in the delivery suites. In the UK and most of the rest of world, most delivery suites do not have ultrasound machines equipped with suitable transvaginal probes, and most obstetric registrars do not have the necessary skills. Studies have used various cervical length cut-off values to define risk, commonly 15, 20 or 25 mm. The negative predictive value is generally stable at each defined length whilst the positive predictive value improves at 15 mm. A cervical length of 15 mm, in a woman symptomatic of preterm labor, has positive predictive values of 28 and 44% for delivery within 48 hours or 7 days with negative predictive values of 97 and 94%, respectively. A cervical length of 15 mm could therefore be reasonably used as a cut-off value at which to offer corticosteroids and *in utero* transfer. Studies in the USA have shown that using this strategy no babies in the group considered to be at low risk of preterm birth are born prematurely without a full course of antenatal corticosteroid therapy, and overall babies in this group had significantly lower rates of exposure to steroids and tocolytics.

Biomarkers: fetal fibronectin, phosphorylated IGFBP-1 and PAMG-1

In the UK, the lack of availability of transvaginal ultrasound machines on labor wards and of an appropriately qualified or experienced clinician to perform the ultrasound, together with the ready availability of bedside testing, means that vaginal biomarker testing is probably the optimal diagnostic test at present. Of the three available methods, detection of fetal fibronectin is the most studied and probably most widely used test. When first introduced these tests were established as being ‘test positive’ at a concentration that conferred a high negative predictive value at the expense of the positive predictive value. In other words, if the test was ‘negative’ the risk of preterm delivery within the next 48 hours or 7–14 days was sufficiently low that in most cases it would be reasonable to withhold steroids or *in utero* transfer. The commonly used ‘qualitative’ fetal fibronectin test uses a ‘test- positive’ cut-off of 50 ng/ml. Here, a positive fibronectin test in a symptomatic woman predicts a risk

of preterm delivery within the next 7 days of approximately 40%, but a negative fetal fibronectin test reduces the risk to less than 1%. Quantitative fetal fibronectin testing has now become available and this has improved the test. Test results can now be interpreted either by using a range of different cut-off values or by direct interpretation of the quantified results. So, for example, as screen-positive cut-off values are increased from the original 50 ng/mL to 200 and 500 ng/mL, the positive predictive value for delivery within 14 days increases from 20% to 37% and 46%, respectively, whilst the negative predictive value only decreases from 98% to 97% and 96%. Using a lower cut-off of 10 ng/mL decreases the positive predictive value to 10% with no effect on the negative predictive value. It is possible to combine the results of transvaginal measurement of cervical length and vaginal fluid fibronectin concentrations to improve risk stratification, provided that facilities for both tests are available. It is essential that the fibronectin test be performed before transvaginal ultrasound examination. Most studies have combined measures of cervical length with categoric fibronectin results based on a cut-off of 50 ng/mL and have demonstrated higher sensitivity and positive predictive value while maintaining high negative predictive value. Where qualitative fibronectin testing is used, it appears that a high fibronectin concentration has a better predictive value than a short cervical length alone. So, for example, a woman with a cervical length below 10 mm but a fibronectin concentration of 10 ng/mL has a very low risk of delivery within 7 days, whereas a woman with a cervical length of 30 mm but a fibronectin concentration above 500 ng/mL is at very high risk. However, either of these two scenarios is likely to be quite rare. The improved predictive value of quantitative fibronectin compared with cervical length is probably a reflection of where on the biochemical pathway to preterm labor the individual woman is. In most cases cervical shortening will precede release of fibronectin into vaginal fluid by several weeks. Fibronectin testing is therefore most useful in identifying the woman at imminent risk of preterm delivery. Measurement of cervical length is probably of better value in identifying women whose risk is more remote. Some studies of interventions to prevent preterm birth which have recruited patients based on fibronectin positivity have been, probably justifiably, criticized for enrolling patients who are too late in the processes of parturition to be helped by the intervention. The development of computed algorithms (e.g.QUIPP, Apple Store) is now allowing fetal fibronectin concentrations to be interpreted as a continuous variable and to provide individualized risk assessment taking into account the patient's history and cervical length measurements if available.

Acute tocolysis

Sympathomimetics

The maximum benefit to the preterm neonate from antenatal corticosteroid administration is from 24 hours to 7 days after the first dose of the course. *In utero* transfer has also been shown to improve neonatal morbidity and mortality and clearly time would be required to move a mother in preterm labor from one hospital to another. Suppression of uterine contractions has therefore been seen as an obvious solution to the problem of preterm labor. The use of tocolytic drugs intended to inhibit uterine contractions began with the introduction of alcohol and then beta-

sympathomimetics into obstetric practice in the 1970s. Early clinical trials suggested that beta-sympathomimetics had great efficacy in inhibiting preterm contractions; there was widespread advertising by the manufacturers and most obstetricians developed the impression that tocolysis (specifically with beta-sympathomimetic drugs such as ritodrine and salbutamol) was an effective therapy for acute preterm labor. This impression was strengthened because of the very high placebo response rate, which implied mistakenly that the drug was being effective. More modern studies have shown that ritodrine will delay preterm delivery in a minority of patients for 24 and 48 hours but that its use is not associated with any improvement in any marker of neonatal morbidity or in neonatal mortality rates. Ritodrine and salbutamol are associated with significant, potentially life- threatening maternal side effects (particularly if given in combination with corticosteroids) that include fluid overload, pulmonary oedema, myocardial ischemia, hyperglycemia and hypocalcemia. Numerous maternal deaths have been reported in which tocolysis using beta- sympathomimetic drugs has played a role. Beta-sympathomimetics as tocolytics are therefore now rarely used in the context of preterm labor, since safer, though not necessarily more efficacious, tocolytic drugs are now available, and their use should probably be completely abandoned. Beta-sympathomimetics continue to have a role in the suppression of excessively frequent or strong contractions stimulated by prostaglandins in the context of induction of labor at term, where short-term use poses few risks.

Non-steroidal anti-inflammatory drugs

The NSAID most widely studied as an acute tocolytic is indomethacin. Earlier relatively small randomized placebo-controlled studies suggested that indomethacin may delay preterm delivery in the short term but the total number of women enrolled in these trials was small. As discussed in previous sections, indomethacin has a major effect on fetal renal function and on the fetal cardiovascular system, in particular on the fetal ductus arteriosus. Use of indomethacin for tocolysis has also been associated with higher incidences of necrotizing enterocolitis, intraventricular hemorrhage and abnormalities in neonatal haemostasias. A series of later studies have all generally been small and of low overall quality. In some network meta-analyses and indirect comparisons indomethacin has appeared to have some benefit in postponement of birth compared with placebo and beta-mimetics and in maternal adverse effects compared with beta-mimetics and $MgSO_4$. However, these types of indirect comparisons (e.g. where indomethacin is compared with salbutamol, salbutamol is compared with $MgSO_4$ and therefore indomethacin can be indirectly compared with $MgSO_4$) are heavily affected by the entry criteria and high placebo response rates in the original studies. There is a lack of longer-term childhood outcomes, limitations of small numbers, and minimal data on safety. At present there is no evidence that indomethacin or any other NSAID has any advantage as a first-line tocolytic over calcium channel blockers or oxytocin antagonists, each of which has a much better maternal and fetal side-effect profile.

Oxytocin antagonists

Although there is no good evidence for an increase in circulating concentrations of oxytocin in either term or preterm labor, both term and preterm labor are associated with an increase in the expression of the oxytocin receptor in the myometrium and oxytocin is synthesized within the uterus itself, in the myometrium and the decidua. This has led to the exploration of drugs which antagonize the oxytocin receptor as tocolytics. At present no specific oxytocin antagonists are available for clinical use, although atosiban, a mixed arginine vasopressin (AVP) and oxytocin receptor antagonist, has a European Medicines Agency licence for the treatment of preterm labor. Atosiban has been the subject of both placebo comparison trials and comparisons with beta-sympathomimetic drugs. The 2000 placebo-controlled trial undertaken in the USA was, to a certain extent, flawed in that randomization at early gestational ages was skewed, resulting in an increase in neonatal deaths amongst very preterm babies whose mothers were treated with atosiban when compared with placebo (Figure 28.7). Atosiban crosses the placenta, but the drug does not accumulate in the fetus with longer infusion rates. Despite its action at the AVP receptor, atosiban does not affect maternal or fetal cardiovascular parameters or fetal oxygenation. The majority of the infant deaths associated with exposure to atosiban were newborns with birthweights below 650 g, suggesting that extreme prematurity not an effect of atosiban was the cause.

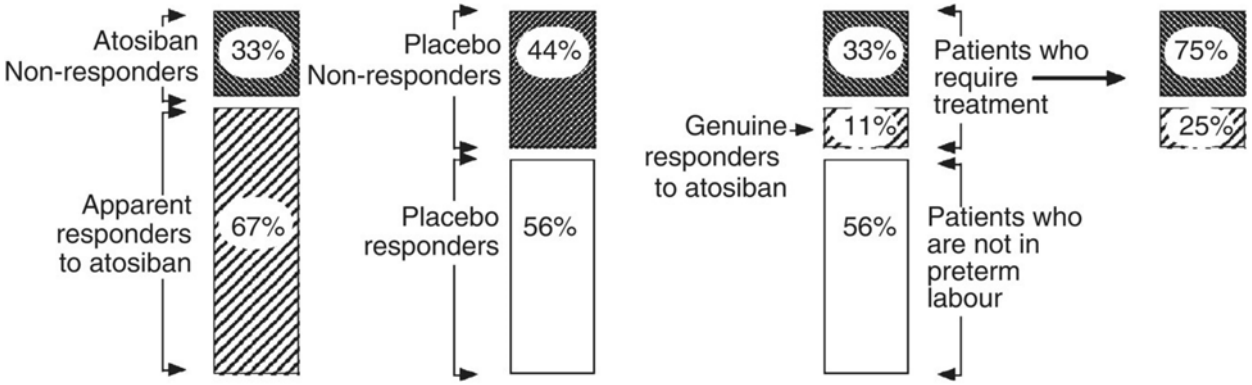


Fig. 28.7 Analysis of the 48-hour outcome data from the placebo-controlled trial of atosiban. Of all patients allocated to atosiban treatment, only 11% showed a genuine clinical response (rather than a placebo response) which represents one-quarter of those with the potential to benefit. This effect applied only in women at 28 weeks' gestational age or greater.

The primary outcome of the placebo-controlled trial (i.e. the time between the initiation of treatment and therapeutic failure, defined as either preterm delivery or need for an alternate tocolytic) showed that atosiban was no different to placebo. For this reason, and because of failure to show overall morbidity or mortality benefit, an FDA license was denied. There were statistically significant differences in the number of women who remained undelivered and did not require an alternative tocolytic at the specific 24- and 48-hour and 7-day time points, although this applied only in women who were beyond 28 weeks' gestation. As with all previous trials of tocolytic drugs, this trial was complicated by a very high placebo response rate. Analysis of the data shows that, for example, at 48 hours post randomization, although 70% of women randomized to receive atosiban appeared to respond to it, in reality the majority of these represented placebo responders. It can be calculated

that only 11% had a genuine clinical response. This represents one-quarter of those women who were genuinely in preterm labor and had potential for a genuine clinical response. The trials comparing atosiban with beta-sympathomimetic drugs showed that atosiban was clinically of equal efficacy to beta-sympathomimetics but with a dramatically improved maternal side-effect profile. However, the clinical response rate to either atosiban or beta- sympathomimetic drugs in these trials was so high (>90%) that it is probable that the majority of patients enrolled in the study were not genuinely in preterm labor. Neither the placebo-controlled trial nor the beta-sympathomimetic comparison trials demonstrated any improvement in any aspect of neonatal morbidity or neonatal mortality associated with the use of atosiban. More recently, it has been found that oxytocin mediates at least two pathways through its receptor, one to stimulate contractions, the other to activate inflammatory pathways and to increase prostaglandin and cytokine synthesis. Atosiban acts as an inhibitor of contractions but as a partial activator of inflammation. A proinflammatory action in a tocolytic is not ideal and may explain the limited efficacy of atosiban. At present, second-generation oxytocin receptor antagonists are in development that are specific to the oxytocin receptor and which do not activate inflammation.

Calcium channel blockers

The central role of calcium in the biochemistry of myometrial contractions led to the exploration of the use of calcium channel blockers, specifically nifedipine, as a tocolytic drug. Because there has been no interest from the pharmaceutical industry in promoting nifedipine for this indication, most of the randomized controlled studies have been comparison trials of nifedipine versus sympathomimetics and other tocolytics. Two small trials comparing nifedipine with placebo or no treatment showed a significant reduction in the risk of birth within 48 hours associated with an increase in maternal adverse effects. The largest number of trials compare nifedipine with beta-mimetics. Meta-analysis of these trials shows that there were fewer maternal adverse effects, an increase in the interval between trial entry and birth, and a decrease in rates of preterm and very preterm birth, RDS, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice and admissions to neonatal intensive care unit. There have been three small and one substantial (APOSTEL III) randomized trials comparing nifedipine with atosiban. The three small trials showed contradictory results. Unlike earlier trials of tocolytic agents, APOSTEL III took advantage of cervical length and fibronectin to better define a population in threatened preterm labor. The study showed that tocolysis for 48 hours with nifedipine or atosiban resulted in similar prolongation of pregnancy and perinatal outcome rates. Discontinuation of either nifedipine or atosiban because of side effects was rare, but rates of discontinuation were no different between the two drugs. At present, the obstetrician (other than in the USA where $MgSO_4$ is still used for its tocolytic action despite evidence that it is ineffective) has a choice between atosiban or nifedipine and it is probably reasonable, in our current state of knowledge, not to use tocolytic therapy at all. More specific oxytocin antagonists are in development, as are drugs which target other receptors, such as prostaglandin receptors. It is probable that the disappointing results of tocolytics in most trials to date is because of poor trial design and, in particular, the high placebo response rates

when contractions alone have been used to diagnose preterm labor. In future trials which are able to target tocolytic drugs more specifically at women genuinely in preterm labor, for example by taking advantage of cervical length measurement or fetal fibronectin testing, may more properly define the potential value of tocolytic therapy.

Antenatal corticosteroid therapy

The potential for antenatally administered corticosteroids to accelerate lung maturity was discovered by Professor Sir Graham ('Mont') Liggins in experiments in which sheep were induced into preterm labor by injection of corticosteroids. Unlike preterm sheep delivered by caesarean section, the sheep in these experiments did not develop fatal RDS. A large number of (human) randomized trials took place during the 1970s and 1980s which, taken together, have shown that a single course of either betamethasone or dexamethasone administered to pregnant women between 24 and 34 weeks gestation who are at risk of preterm delivery within 7 days has a beneficial significant effect on neonatal morbidity and mortality. Although the pediatric use of surfactant has had a major impact on the incidence and consequence of RDS, nevertheless antenatal corticosteroid therapy is still associated with a reduction in neonatal mortality, principally due to a significant reduction in rates of RDS and intraventricular hemorrhage. Antenatal corticosteroids have a receptor-mediated effect on all the components of the surfactant system in type 2 pneumocytes. They also have effects on the structural development of the lungs, lead to accelerated maturation of the fetal intestine and have effects on the myocardium and on catecholamine responsiveness, which may explain the reduced incidence of necrotizing enterocolitis and intraventricular hemorrhage seen in extremely preterm infants that appear to be independent of the effect on RDS. Women who are considered to be at risk of preterm delivery at between 24 and 35 weeks of gestation should be targeted for a single course of antenatal corticosteroids. Antenatal corticosteroids should also be considered for women from 23 weeks onwards, based on estimated fetal weight and parental wishes. Whilst antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver from 24 hours and up to 7 days after administration of the second dose of antenatal corticosteroids, there is an effect on neonatal death rates even if delivery is within the first 24 hours so steroid should still be given even if delivery is expected in less than 24 hours. A single course of corticosteroids does not appear to be associated with any short-term maternal or fetal adverse effects, with the exception of the destabilization of blood sugar control in diabetics or impaired glucose tolerance in pregnancy. Diabetes mellitus should not be considered a contraindication to antenatal corticosteroid treatment for fetal lung maturation, particularly because RDS is more common in the babies of diabetic mothers. Women with impaired glucose tolerance or diabetes who are receiving steroids should have additional insulin according to an agreed protocol and be closely monitored. The dramatic effects of a single course of corticosteroids unfortunately led to the routine prescription of multiple courses of steroids, often at weekly intervals, in women deemed to be at risk of preterm delivery, especially those with multiple pregnancies. Concerns about the long-term consequences of recurrent exposure to high-dose steroids, namely the adverse effects

on development and behavior, has generally led to an abandonment of this policy. Although one or more repeat courses of corticosteroids is associated with reduced severe lung disease and serious infant morbidity, repeated courses of steroid are associated with an increased risk of intrauterine growth restriction. The challenge for the obstetrician is therefore to use a combination of the clinical history, markers of infection or inflammation, the results of cervical length measurements and fetal fibronectin or other biomarkers to refine the estimate of risk of preterm delivery in any individual woman to correctly target a course of corticosteroids prior to delivery, and to reduce the number of repeat courses ideally to one or none. Both dexamethasone and betamethasone have been explored in randomized trials, with each having similar effects on RDS rates. Studies in France suggested that betamethasone reduced the incidence of periventricular leukomalacia whereas dexamethasone had no such protective effect; however, this may be explained by the presence of sulfating agents used as preservatives in French preparations of dexamethasone. A historical cohort study used multivariate logistic regression analysis to compare the two steroid-treated groups with each other, finding that the risk of neonatal death was lower with betamethasone than with dexamethasone. In other studies dexamethasone has been associated with a decreased incidence of intraventricular hemorrhage compared with betamethasone. At present, there is no clear evidence of benefit of dexamethasone over betamethasone or vice versa. Therefore, either betamethasone 12 mg i.m. in two doses or dexamethasone 6 mg i.m. in four doses are the steroids of choice to enhance lung maturation.

Magnesium sulfate

Prior to the 1980s, $MgSO_4$ was widely used in the USA in the intrapartum management of pre-eclampsia and eclampsia and the clinical impression that $MgSO_4$ made induction of labor more difficult led to its evaluation as a tocolytic agent. With the withdrawal of beta- sympathomimetic drugs from the American market and the failure of atosiban to obtain FDA approval, there are no licensed tocolytic drugs available for the American obstetrician to use and $MgSO_4$ is therefore in common use. However, randomized placebo-controlled trials of $MgSO_4$ show no significant short-term delay of delivery, increase in birthweight or difference in perinatal mortality when compared with placebo. $MgSO_4$ is ineffective at delaying birth or preventing preterm birth, and has no apparent advantages for neonatal and maternal outcomes when used as a tocolytic agent. However, studies where $MgSO_4$ has been compared with sympathomimetics or indomethacin have suggested equal efficacy. These two apparently contradictory findings can probably be explained by the lack of power of the studies to detect a significant difference between drugs with little or no efficacy but a high placebo response rate. In the late 1990s it began to become apparent that infants born to mothers given $MgSO_4$ either to prevent eclampsia or for tocolysis appeared to have a reduced risk of cystic periventricular leukomalacia and cerebral palsy. Since that time a series of randomized controlled trials has been conducted which confirm that the risks of both cerebral palsy and substantial gross motor dysfunction are reduced in the infants of

women given $MgSO_4$ just prior to preterm delivery. The beneficial effects of $MgSO_4$ appear to be greatest in women at early gestations, particularly between 24 and 30 weeks. There is probably little or no effect in women beyond 34 weeks. Every effort should therefore be made to offer intravenous $MgSO_4$ to women at risk of preterm delivery before 30 weeks, and if possible, to those up to 32 weeks. The mechanism of action of $MgSO_4$ in the neonatal brain is not clearly established. It may act by blocking *N*-methyl-D-aspartate (NMDA) receptors which mediate glial injury processes in hypoxia–ischemia. $MgSO_4$ may also act to block calcium influx into damaged cells, to inhibit vasoconstriction, to reduce cytokine-mediated cell damage, and to interact with a wide range of cellular functions through its complex with ATP. $MgSO_4$ has the advantage over corticosteroids of being effective when administered close to the time of preterm delivery. As with its use in the context of pre-eclampsia, $MgSO_4$ has the potential for toxicity in the mother, leading to nausea and vomiting, lethargy, cardiac dysrhythmia, hypotension, urine retention, and respiratory and cardiac arrest. It is therefore essential that the same safeguards are put in place when it is used for cerebral palsy prophylaxis. The optimal dosing regimen for $MgSO_4$ has not been determined. Different studies have used different protocols, although these were commonly based on the protocols that would be used in pre-eclampsia, or where the drug is used as a tocolytic. A typical protocol would be a 4-g bolus followed by 1 g/hour i.v.

Antibiotics

Analysis of the use of antibiotics in symptomatic preterm labor with intact membranes in women with no clinically defined infection is dominated by the 2001 ORACLE I trial. This showed that administration of antibiotics to women in spontaneous preterm labor with intact membranes does not delay delivery or improve any aspect of neonatal morbidity or mortality. The only short-term positive health benefit is a reduction in maternal infection rates. However, a follow-up study which examined the effect of antibiotics given during pregnancy to mothers in threatened preterm labor on childhood outcomes at 7 years showed an increase in the risk of cerebral palsy associated with antibiotic use. Surprisingly, this was principally in babies who were actually born at term. Taken together these data show that antibiotics should not be prescribed to women in uncomplicated preterm labor with no evidence of infection. However, it is important to emphasize that there are associations between preterm labor, chorioamnionitis, pneumonia, pyelonephritis and lower urinary tract infection. Care needs to be taken to exclude these diagnoses which do require antibiotic therapy to reduce the risk of complications of puerperal sepsis.

Management of inevitable preterm delivery

Rates of neonatal morbidity and mortality are higher in babies transferred *ex utero* to neonatal intensive care units compared with those born in the tertiary referral center. Every effort should therefore be made to transfer a woman to an obstetric unit linked to a neonatal intensive care unit prior to a preterm delivery. The

introduction of fetal fibronectin testing has reduced the numbers of unnecessary *in utero* transfers.

Cardiotocography monitoring

Except at the extremes of prematurity (perhaps below 26 weeks) there should be continuous electronic fetal heart rate monitoring once preterm labor is clearly established in most cases. The value of cardiotocography (CTG) in preterm labor is less well established than at term. Physiological control of fetal heart rate differs in the preterm fetus compared with the fetus at term, making CTG interpretation difficult. The fetal heart rate baseline is higher, averaging 155 bpm before 24 weeks compared with 140 bpm in a term fetus. Prematurity may normally be associated with a reduction in fetal heart rate baseline variability and be decreased secondary to the effect of fetal tachycardia but without significant hypoxia. The normal sleep–wake cycles seen at term may be absent or less common. Before 30 weeks the frequency and amplitude of accelerations are reduced, whereas fetal heart rate decelerations without contractions often occur in the healthy preterm fetus between 20 and 30 weeks of gestation. Fetal monitoring in labor should be individualized, taking into account the context of preterm delivery, gestational age and estimated fetal weight, the likelihood of chorioamnionitis and any other complications, the overall prognosis for the neonate, and the wishes of the parents. Modern ultrasound-based CTG machines have rendered the use of fetal scalp electrodes largely redundant but they should particularly be avoided in babies below 34 weeks' gestational age.

Vaginal or caesarean section delivery

There is no evidence of benefit for routine delivery by caesarean section where the presentation is cephalic. However, hypoxia is a major risk factor for the development of cerebral damage and there should therefore be a relatively low threshold for delivery by caesarean section in the presence of abnormal fetal heart rate patterns. Nevertheless, preterm labor is usually rapid. The fetal head will be small, and therefore there will be a complete absence of the relative cephalopelvic disproportion seen at term, meaning that there is no need for molding of the fetal head. In many cases the cervix is already ripe and effaced before the onset of contractions. The preterm delivery of a breech continues to be an obstetric dilemma. Although it is now established that elective caesarean section is preferable for the term breech, it has proved impossible to undertake randomized trials of caesarean section for the preterm breech. One potential disadvantage of planning to deliver the preterm breech (or indeed cephalic presentation preterm) by elective caesarean section is the high incidence of 'threatened' preterm labor which does not lead to preterm delivery. An aggressive policy of delivering preterm babies by caesarean section has the potential to lead to iatrogenic preterm deliveries. At the other end of the spectrum, caesarean section before term where the breech is already in the vagina may be more traumatic than a vaginal delivery. At present, until further evidence becomes available the mode of delivery of the preterm breech will need to be made on a case-by-case basis by the obstetrician at the time. There is no evidence of benefit from the old practice of elective forceps delivery to protect the fetal head during preterm delivery and episiotomy is rarely required. If instrumental delivery is

required for the preterm infant below 34 weeks, ventose should be avoided. It is usually easy to rotate a preterm fetal head to an occipital-anterior position manually, or it can be done using Kielland's forceps by those who still have the skill. There is now good evidence for the benefit of delayed cord clamping and in waiting at least 30 seconds but no longer than 3 min if the mother and baby are stable. If the preterm baby needs to be resuscitated or there is significant maternal bleeding, the umbilical cord can be briefly milked in the direction of the neonate and then clamped more quickly. If delivery by caesarean section is required, there may be a need to perform a classical caesarean section through a vertical incision in the uterus, particularly at very preterm gestational ages when the lower segment of the uterus is poorly formed. Occasionally, an incision initially made in the lower segment proves to be insufficient for delivery. In these cases, the incision can be converted to a J-shaped incision. Particularly at the limits of viability, delivery should be performed has in traumatically as possible, ideally delivering the baby *en caul* in intact membranes. This greatly minimizes the risk of fetal trauma, and nautical folklore has it that a child born *en caul* will never drown at sea.

MATERIALS FOR ACTIVATION OF STUDENTS DURING THE LECTURE: QUESTIONS, SITUATIONAL TASKS, ETC.

TEST TASKS

1. Patient '30 admitted to the gynecology department with complaints of recurrent pulling abdominal pain, blood spotting from the genital tract. In the history of two spontaneous abortions. Vaginal study: cervix up to 3 cm, cyanotic, the outer jaws pass fingertip, uterus is soft increased to 6.7 weeks of pregnancy, applications are not palpable, vaults deep. Last menstruation 2 months ago. What should appoint a more accurate diagnosis?

+A. Pelvic ultrasound
B. Measurement of basal temperature
C. Determine the contents of HCG in urine
D. Identify the 17 level in the urine ketosteroids
E. All of the above

2. Patient '22 admitted to the gynecology department with complaints of recurrent pulling pain in the abdomen and in the lumbar region, baldly bleeding from the genital tract. Vaginal study: cervix length 2.5 cm, cyanotic, the outer jaws passes fingertip, uterus is soft, increased to 6-7 weeks. pregnancy, applications are not defined, vaults deep. Last menstruation 2 months ago. What is the most likely diagnosis?

A. menstrual disorders
+ B. Threatened abortion
C. Abortion run
D. Incomplete abortion
E. Ectopic Pregnancy

3. Primigravida in the period 11-12 weeks of gestation complains of intense cramping abdominal pain and significant bleeding from the genital tract. Abdomen

soft, painless. Vaginal cancer research body increased to 11-12 weeks of pregnancy, periodically tones. Cervical canal passing to 2 cm. Profuse bleeding. What is the most likely diagnosis?

A. Threatened abortion
+ B. Spontaneous abortion
C. Incomplete abortion
D. Full abortion
E. Cervical pregnancy

4. Primigravida admitted to the gynecology department with complaints of recurrent abdominal pain and bleeding from the genital tract. Vaginal study: cervix length of 2.5 cm, cyanotic, the uterus passes fingertip, uterus is soft consistency, increased to 6.7 weeks of pregnancy, applications are not defined, the vault free. Tactics doctor?

+A. To prescribe hormone therapy
B. Assign antibiotic therapy
C. Assign uterotonic therapy
D. To appoint sedative therapy
E. Dilation and Curettage

5. Examining the patient in the women's clinic, the doctor discovered that the uterus is increased to 5-6 weeks of pregnancy, asymmetric in the left corner of the uterus palpable protrusion. Uterus soft consistency, but decreased during the study become hard and then again become soft. What is the most likely diagnosis?

+A. The uterine pregnancy
B. Threatened abortion
C. Abortion run
D. Uterine fibroids
E. Ectopic Pregnancy

6. Women, 28 years old admitted to the gynecology department complaining of abdominal pain left and minor bleeding during the last 2 days. 2 In the history of childbirth. Last menstruation 6 weeks ago. Menstrual disorders still have not watched. Protected from pregnancy using intrauterine device. BP during hospitalization 110/70 mmHg, hemoglobin 124 g / l. What is most informative method of investigation?

A. Radiography “Sella turcica”
B. Determination of HGH in urine
C. Functional diagnostic tests
+ D. Transvaginal pelvic ultrasound
E. Dilation and curettage

7. Primigravida at term of gestation 5-6 weeks. There was spontaneous abortion at home. Vaginal study: external genitalia are developed, female type, with no signs of inflammation, free vagina, cervix formed, the cervical canal passes fingertip, uterus firm, painless palpation slightly increased in size. Applications are not palpable uterine, vaginal vault free. What is the most likely diagnosis?

A. Threatened abortion
B. Abortion run
C. incomplete abortion

+D. Complete abortion
E. Cervical pregnancy
8. Patient, 24 years old delivered to hospital by ambulance with complaints of cramping abdominal pain, heavy with clots bleeding from the genital tract, weakness. BP 100/60 mm Hg. Art., pulse 90 beats / min. Last normal menstruation 2 months ago. During examination of the cervix in the speculum defined remnants of embryonic tissue. Bimanual examination: uterus size is increased to 6 weeks of pregnancy, painless, cervical canal passes finger. What is the most likely diagnosis?
A. Abortion run
+B. Incomplete abortion
C. Complete abortion
D. cervical abortion
E. dysfunctional uterine bleeding
9. Pregnant '22 was registered with the LCD on 11-12 weeks of pregnancy. In recent days hauling felt pain in the lower abdomen, but the doctor is not addressed. An hour ago, there were cramping abdominal pain and bleeding. Vaginal study: vagina filled with blood clots, uterine cervix exposed to 2 cm, the uterus increased to 11-12 weeks of pregnancy, dense. Bold blood, abundant. What are the doctor's tactics?
A. Observations
B. hormone therapy (progesterone)
C. tocolysis
D. Blood transfusion
+ E. Curettage
10. Secondi Para at gestation term 18 weeks, was admitted to the hospital with complaints of recurrent pulling pain in the abdomen and in the lumbar region, dark bloody discharge from the genital tract, nausea, weakness. Vaginal study: uterus increased to 12 weeks of pregnancy. With ultrasound, fetal cardiac activity is not visualized, the displacement of the skull bones, spine bending angulate fetus. What is the most likely diagnosis?
A. Threatened abortion
B. Abortion run
C. incomplete abortion
D. Full abortion
+ E. missed abortion
11. A pregnant 26-year-old woman was admitted to a hospital for abdominal pain and bleeding from the genital tract. Bimanual examination revealed that uterus was the size of 9 weeks of pregnancy, the cervical canal let a finger through. Fetal tissues could be palpated in the orifice. There was moderate vaginal bleeding. What is the tactics of choice?
+A. Instrumental extraction of fetal tissue
B. Surveillance
C. Administration of hormones
D. Hemostatic and antianemia therapy
E. Therapy for the maintenance of pregnancy

12. A 36-year-old female presented to a gynecological hospital with a significant bleeding from the genital tract and a 1-month delay of menstruation. Bimanual examination revealed soft barrel-shaped cervix. Uterus was of normal size, somewhat softened. Appendages were unremarkable on both sides. Speculum examination revealed that the cervix was cyanotic, enlarged, with the the external orifice disclosed up to 0,5 cm. Urine HCG test was positive. What is the most likely diagnosis?
+A. Cervical pregnancy
B. Uterus gestation
C. Abortion in progress
D. Threatened miscarriage
E. Ectopic pregnancy

13. A pregnant woman is 28 years old. Anamnesis: accelerated labor complicated by the II stages degree cervical rupture. The following two pregnancies resulted in spontaneous abortions at the terms of 12 and 14 weeks. On mirror examination: the uterine cervix is scarred from previous ruptures at 9 and 3 hours, the cervical canal is gaping. On vaginal examination: the cervix is 2 cm long, the external orifice is open 1 cm wide, the internal orifice is half-open; the uterus is enlarged to the 12th week of pregnancy, soft, mobile, painless, the appendages are without changes. What diagnosis would you make?
+A. Isthmic-cervical insufficiency, habitual non carrying of pregnancy
B. Threatened spontaneous abortion
C. Incipient abortion, habitual non carrying of pregnancy
D. Cervical hysteromyoma, habitual non carrying of pregnancy
E. Cervical pregnancy, 12 weeks

14. A 10 weeks of pregnant woman was admitted to a hospital for recurrent pain in the lower abdomen, bloody discharges from the genital tracts. The problems developed after a case of URTI. The woman was registered for antenatal care. Speculum examination revealed cyanosis of vaginal mucosa, clean cervix, open cervical canal discharging blood and blood clots; the lower pole of the gestational sac was visible. What tactics should be chosen?
+A. Curettage of the uterus
B. Pregnancy maintenance therapy
C. Expectant management, surveillance
D. Hysterectomy
E. Antiviral therapy

15. A pregnant woman is 28 years old. Anamnesis: accelerated labor complicated by the II stages of degree cervical rupture. The following two pregnancies resulted in spontaneous abortions at the terms of 12 and 14 weeks. On mirror examination: the uterine cervix is scarred from previous ruptures at 9 and 3 hours, the cervical canal is gaping. On vaginal examination: the cervix is 2 cm long, the external orifice is open 1 cm wide, the internal orifice is half-open; the uterus is enlarged to the 12th week of pregnancy, soft, mobile, painless, the appendages are without changes. What diagnosis can be made?
A. Cervical hysteromyoma, habitual non carrying of pregnancy

B. Incipient abortion, habitual non carrying of pregnancy
+ C. Isthmic-cervical insufficiency, habitual non carrying of pregnancy
D. Threatened spontaneous abortion
E. Cervical pregnancy 12 weeks

16. A woman with the pregnancy term of 8 weeks complains of elevated temperature up to 37.6°C, skin rash that can be characterized as macular exanthema, enlargement of posterior cervical and occipital lymph nodes, small amount of bloody discharge from the genital tracts. She was examined by the infectious diseases specialist and diagnosed with rubella. What tactics should the obstetrician-gynecologist choose?

+ A. Abortion
B. Treatment of incipient abortion
C Prescription of hemostatic therapy
D. Prescription of antibacterial therapy
E. Prescription of antiviral therapy

17. A 25-year-old woman was brought into the gynecological department with profuse bloody discharge from her genital tracts. She is 12 weeks pregnant; the pregnancy is planned. Within the last 3 days she was experiencing pains in her lower abdomen that eventually started resembling cramps, she developed bleeding. Her skin is pale, pulse -88/min., blood pressure -100/60 mm Hg, body temperature -36.8°C. Vaginal examination: the uterus size corresponds with 11 weeks of pregnancy, the cervical canal allows inserting 1 linger and contains fragments of the fertilized ovum, the discharge is bloody and profuse. What is the most likely diagnosis?

+ A. 12-week pregnancy, spontaneous abortion in progress
B. 12-week pregnancy, threatened spontaneous abortion
C. Full-term pregnancy, term labor
D. Disturbed menstrual cycle, hyper polymenorrhagia
E. Disturbed menstrual cycle, amenorrhea

LECTURE 4
"Hypertensive disorders in pregnancy. Preeclampsia. Eclampsia. Emergency care"

RELEVANCE: Etiology and pathogenesis, modern diagnostic methods, volumetric survey of patients, clinical features, classification of preeclampsia and eclampsia are basic to understand here to provide qualified emergency care, modern principles of prevention and medical rehabilitation of the patients. Unless well studied, this can make impossible to master physiological and pathological obstetric care.

LEARNING OBJECTIVE is to gain basic knowledge about the etiology, pathogenesis, the clinic, methods and algorithm for diagnosing preeclampsia and eclampsia in pregnant women. Get knowledge about modern treatment and prevention principles of pregnant women with preeclampsia during pregnancy and principles of rehabilitation. Develop a special vigilance in the prevention and early diagnosis preeclampsia and eclampsia of pregnant women in students. Form a sense of moral and legal responsibility for the timeliness and quality of medical care obstetric patients. To familiarize students with the contribution of Ukrainian midwifery school issues prevention, diagnosis of preeclampsia and eclampsia of pregnant women, treatment and rehabilitation patients.

BASIC CONCEPTS: Etiology and pathogenesis of preeclampsia and eclampsia. Modern diagnostic methods for preeclampsia and eclampsia, volumetric survey of patients. Clinic of preeclampsia and eclampsia. Classification of preeclampsia and eclampsia. Principles of pregnant women with early gestosis, preeclampsia and eclampsia. Emergency care. Modern principles of prevention preeclampsia and eclampsia, medical rehabilitation patients.

EDUCATIONAL MATERIALS

Early gestosis

The concept of "early gestosis" exists only in the practice of obstetricians - gynecologists CIS. In obstetric practice of foreign countries such thing does not exist, there is state assessed as 'minor' complications of pregnancy, or "unpleasant symptoms during pregnancy". But in the HIC-10, section XV, topic O21 includes vomiting varying degrees of severity during pregnancy, and headings O26 and O28 provide other conditions associated with pregnancy. We therefore consider it appropriate to consider in a separate section of the particular state of pregnancy, under the heading "early gestosis".

The pathology of pregnancy is divided into two groups (for the clinical course):

1. Early gestosis, which often occurs - vomiting of pregnant, excessive salivation, pruritus gravidarum.
2. Early gestosis, which is rare - dermatosis of pregnant, cholestatic hepatosis pregnancy, acute liver steatosis of pregnant, tetania gravidarum, chorea gravidarum, osteomalacia gravidarum, bronchial asthma of pregnancy.

Etiology and pathogenesis of early gestosis.

To explain the causes of early gestosis suggested many theories (toxemic, allergic, endocrine, neurogenic, psychogenic, immune, etc.).
In modern theories of early gestosis is considering as a consequence of violations of neuro-vegetative-immuno-endocrinic-metabolic-regulation, in which the leading role played by the functional state of CNS.
It lasted from excessive impulse fetal egg causes excessive irritation areas of the hypothalamus, brain stem and entities that are involved in the regulation of autonomic functions and inhibition of neural processes in the cerebral cortex. As a consequence - the predominance of excitatory processes in the brain stem (in particular, vomiting center).
Risk factors of early gestosis
• Spouse or acquired deficiency of the neuroendocrine regulation of adaptive responses (hypoxia, infection, intoxication, violation of the regime in childhood and adolescence, and the like).
• Extragenital diseases.
• Violations of the function of the nervous system, stress situations.
• Past medical genital organs, which can cause changes in the receptor apparatus of the uterus and the occurrence of pathological impulse to the CNS.

Vomiting of pregnant
Vomiting of pregnant (emesis gravidarum) is a complex clinical syndrome. The act of vomiting - one of the manifestations of the disease, which develops diarrheal, nimble, secretory, sensory, vascular and other disorders.
In terms of severity, light vomiting (less than 5 times a day), moderate (5 to 10 times) and severe vomiting (hyperemesis gravidarum) with metabolic disorders (more than 10 times a day). It should be noted that in 50% of pregnant women in early pregnancy occurs "morning vomiting, which does not have a pathological nature and does not require medical treatment.

Degree	Status	Frequency of vomiting	Weight loss	HR	laboratory research
I. Light (neurosis phase)	Satisfactory	Up to 5 times	Not more than 3 kg	Norm	Norm
II. Moderate (toxicosis phase)	Relatively satisfactory	6 -10 times	More than 3 kg	Up to 100	Acetone in the urine ++

III. Severe (dystrophy phase)	Severe	Up to 25 times and more	8 - 10 kg and more	Above 100	Acetone in the urine ++++

In determining the severity of the disease determine the clinical manifestations: State of the pregnant woman, dry skin, yellow sclera and skin, the presence or lack of appetite, salivation, nausea, vomiting frequency and intensity, the curve of weight loss, dehydration, heart rate, blood pressure, sub-febrile temperature, value diuresis. Assessment of the severity of vomiting pregnant includes host and the results of laboratory tests: specific gravity of urine, the presence of ketonuria, the presence of acetonitrile, well in urine, the level of bilirubin, creatinine in the blood.

To diagnose and monitor the effectiveness of treatment conducted the following studies:

• control of body weight;
• control of diuresis;
• The dynamics of BP;
• Determining hematocrit and hemoglobin;
• urine (specific gravity, acetone, ketone bodies, protein);
• biochemical study of the blood (bilirubin and its fractions, liver enzyme, creatinine);
• Determining the level of electrolytes in the blood (K, Na, Cl);
• identification of acid-base balance Blood (KFL).

Differential diagnosis of vomiting pregnant should be conducted with the following diseases: food poisoning, gastritis, pancreatitis, pyelonephritis, cholelithiasis, hepatitis, appendicitis, meningitis, brain tumors, etc.

Treatment of vomiting pregnant

A large number of recommended treatments reflect the majority of theories that explain the causes of vomiting pregnant. But uncontrolled use of these treatments for early gestosis in some cases may be harmful, taking into account the fact that in early pregnancy occurs embryogenesis.

Mild vomiting. It is recommended not to hospitalize pregnant women with mild vomiting. We recommend correction of dietary intake: minor (5-6 times a day), balanced nutrition, drink vitamins. Patients were given a light meal, which is well absorbed (biscuits, mashed potatoes, tea, cocoa, coffee, lean meat, fish, eggs, butter, etc.). Take her trail, lying, frequently and in small portions, preferably in chilled.

Non-traditional methods of treatment can be used: reflexology, hypnosis, central electroanalgesia, homeopathic therapy, and others.

Moderate and severe vomiting: pregnant woman needs hospitalization and medical treatment.

Before the reception ability to hold food, medicines should be entered only parenterally. For the influence of the central nervous system as the main pathogenetic factor, to harassment excitability of the vomiting center designate:

Etaperazin to 0,002 g, orally, 3-4 times a day, 10-12 days (if the patient holds the tablets); torekan by 1.0 ml intramuscular injection, or 6.5 mg in the form of tablets or rectal suppositories 2 -3 times a day; droperidol on 0,5 - 1,0 ml intramuscularly 1-3 times a day; cerucal 10 mg intramuscularly or orally.

To eliminate hypoproteinemia and dehydration, intravenous targeted administration of protein (plasma), Ringer-Locke solution is necessary. In general, all infusions are carried out only according to indications based on laboratory tests. The amount of fluid is determined by the state of the water balance.

Complication: Excessive vomiting can lead to dehydration, exhaustion, and Mallory-Weiss syndrome (rupture of the stomach lining). In some cases, it is necessary to prematurely terminate the mother's pregnancy. The indication for this is the lack of effect of treatment within 7-10 days, threatening the life of the mother, stable tachycardia, hyperthermia, proteinuria and progressive cylindruria, the presence of jaundice and acetone in the urine.

Prevention of early preeclampsia is the early identification of pregnant women at risk for early development of preeclampsia, and their rehabilitation, treatment of comorbidity, and early registration of pregnancy.

Drooling (*hyper salivation) of *pregnant woman.

Drooling (ptyalismus) observed at pukes, and sometimes self-expression and preeclampsia. The number of saliva during hyper salivation may reach 1.0 liters per day. Drooling does not involve serious disturbances in the body, but also suppresses the psyche of patients, causes maceration of the skin and mucous membrane of the lips. Sometimes, in order to reduce the secretion of the salivary glands prescribed intramuscular injection of atropine on 0,5 ml 0,1% solution of 2 times a day. Mouth rinse with infusion of sage, mint, chamomile, oak, measles and other astringent agents. Termination of pregnancy in this pathology is not necessary.

Pruritus gravidarum

Itching of pregnancy (pruritus gravidarum) which can be restricted by the region of the vulva and spread all over the body causing irritability and disturbances of sleep is the most frequent form of dermatosis.

Itching of pregnant women should be differentiated with allergic reactions, mycoses, trichomoniasis, diabetes mellitus and helminthoses.

Antihistamine and sedative drugs, vitamins of B group and ultraviolet radiation are used for the treatment.

Rare forms of gestosis

Dermatosis of pregnant women is a group of diseases that arise in connection with pregnancy and disappear after its termination. Prevalence adds 1 in 200 pregnancies. Skin diseases during pregnancy depend on the functional imbalance between the cortex and the subcortex, increased excitability of the autonomic nervous system, which is accompanied by disturbances in the innervation of the skin, metabolic, microcirculatory changes in it. Dermatosis of pregnant women manifests itself in the form of itching of the skin, less often in the form of eczema, urticaria, erythema, papular rashes. The disease does not affect the condition of the fetus.

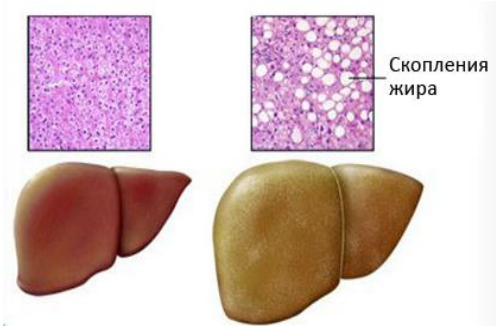
Treatment of dermatosis: food with limited fats and proteins, drugs that regulate the function of the nervous system and metabolism, antihistamines, rarely systemic or local corticosteroids.

Pemphigoid of pregnant women is a liquid but severe pathology, which is accompanied by premature birth, fetal growth retardation, fetal distress, and increased perinatal mortality. Itchy rashes first appear on the skin of the abdomen near the navel, and then spread to the limbs, arms and reaching the feet. First, these are papules and plaques, after 2 weeks they transform into vesicles and dense vesicles. Diagnosis is based on the detection of complement in the basement membrane of the epidermis. Treatment: Topical 1% hydrocortisone cream or systemic corticosteroids and sedative antihistamines.

Pregnancy with **cholestatic hepatosis** can occur at different stages of pregnancy, but most often occurs in the third trimester and occurs in 1 in 2000 pregnant women. The pathogenesis of this disease has not been studied sufficiently. Factors such as the inhibitory effect of progesterone on the function of cholexcretion, increase in cholesterol production, a decrease in the tone of the biliary system, and an increase in the viscosity of bile can be significant in origin. The onset of jaundice is preceded by the spread of intense itching of the skin. The general situation of patients with cholestatic hepatosis of pregnant women does not change significantly. During laboratory examination, moderate leukocytosis, neutrophilosis, as well as something more pronounced than in uncomplicated pregnancy, an increase in WIDE, is determined. The content of bilirubin in the blood is increased (up to 90 mmol / l) and quickly returns to normal after delivery. Alkaline phosphatase levels rise. There was no increase in liver enzymes such as ALT and AST.

A differential diagnosis should be made when the liver and biliary tract are damaged by mechanical or infectious factors, as well as a result of metabolic disorders. Jaundice may develop as a result of severe intoxication in severe early preeclampsia. Treatment of cholestatic hepatosis consists in the appointment of a balanced diet (diet No. 5) and in the use of funds that help eliminate itching. 3 of this order to use cholestyramine 12-15 mg / day (salt binds bile acids). The use of ursodeoxyholic acid improves liver function. In some cases, this may become necessary when terminating a pregnancy due to an exacerbation of the clinical manifestations of the disease and damage to the fetus. It is advisable to prescribe vitamin K a week before the scheduled birth to reduce the risk of postpartum hemorrhage.

Acute liver steatosis of pregnant women is one of the most severe forms of preeclampsia, which often occurs in late pregnancy (33-40 weeks) with a prevalence of 1 per 100,000 pregnant women and is characterized by a very acute onset and high mortality. Morphologically, this is a pronounced fatty degeneration of the hepatocyte in the absence of signs of necrosis. In the clinical course of fatty degeneration of the liver, two stages are distinguished. Before jaundice, there is abdominal pain, weakness, headache, nausea, debilitating heartburn, itchy skin. Jaundice aggravates the symptoms of hepatic and renal failure, intoxication, encephalopathy, DIC syndrome develops, and fetal death often occurs. The immediate cause of death in a pregnant woman is cerebral edema and severe bleeding coagulopathy.



Treatment of this serious complication is correction of coagulopathy and electrolyte imbalances, cardiorespiratory support, and delivery as feasible by the vaginal route, if possible.

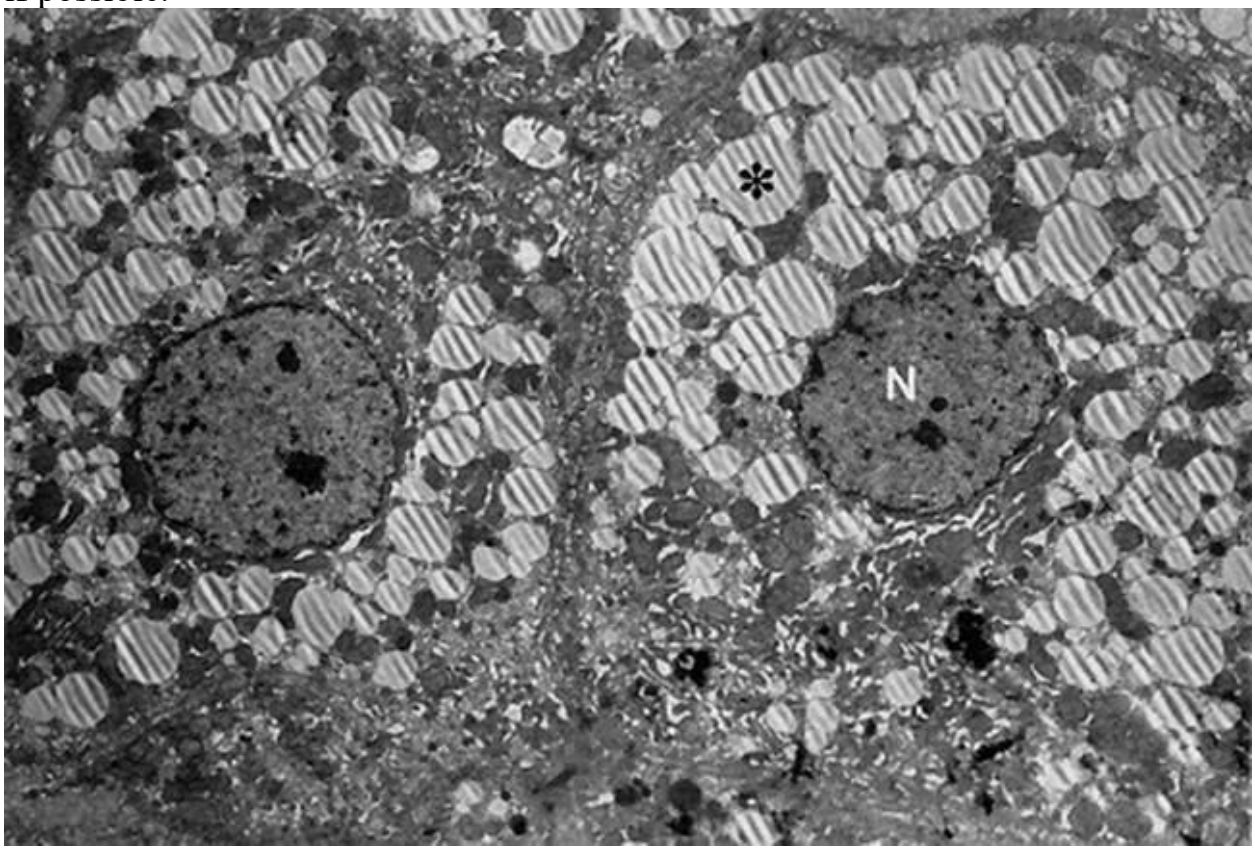


Fig.1 Fatty liver of pregnancy. Electron photomicrograph of two hepatocytes containing numerus microvesicular fat droplets (*). The nuclei (N) remain centered within the cells, unlike with the case of macrovesicular fat deposition. (Courtesy of Dr. Don Wheeler.)

Bronchial asthma of pregnancy

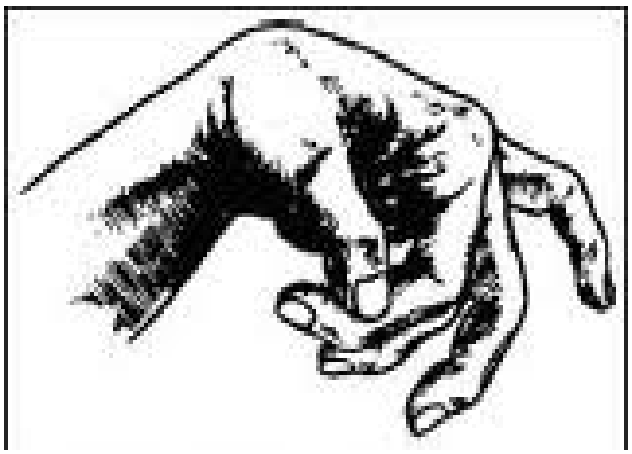
Occurs rarely but it is difficult. The main symptoms of asthma in pregnant women are attacks of suffocation and chronic dry cough. Pregnant bronchial asthma should be distinguished from the usual form bronchial asthma which is normally present before the beginning of pregnancy.

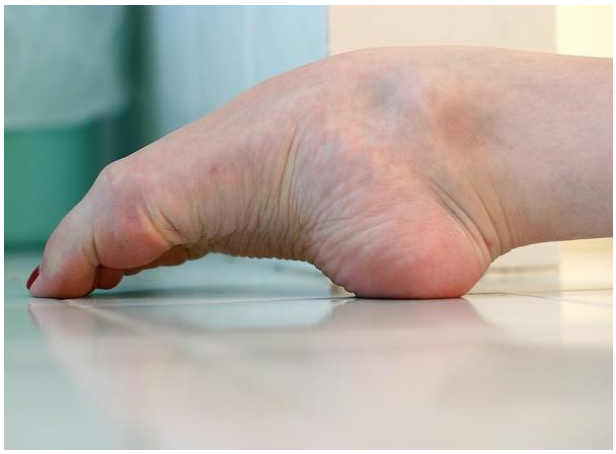
Treatment includes appointment

- preparations of calcium,
- sedatives,
- vitamins.

Tetania gravidarum

Tetany of pregnancy (tetania gravidarum) can manifest by convulsions of the upper ("obstetrician's hands") or lower extremities ("ballerina's leg"), face ("fish's mouth"). Disease is related to the reduction of function of parathyroid glands, disturbance of calcium metabolism, rheumatism. Parathyreoidin, calcium preparations, vitamin of B groups, calciferol (D) and tocopherol acetate (E) are used. During the severe course of the disease or ineffective treatment it is recommended to make an abortion.

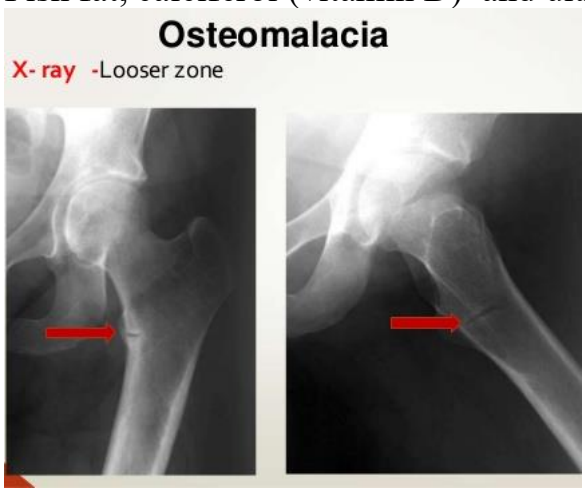




Chorea gravidarum is the term given to chorea occurring during pregnancy. This is not an etiologically or pathologically distinct morbid entity but a generic term for chorea of any cause starting during pregnancy. Chorea is an involuntary abnormal movement, characterized by abrupt, brief, nonrhythmic, nonrepetitive movement of any limb, often associated with no patterned facial grimaces.

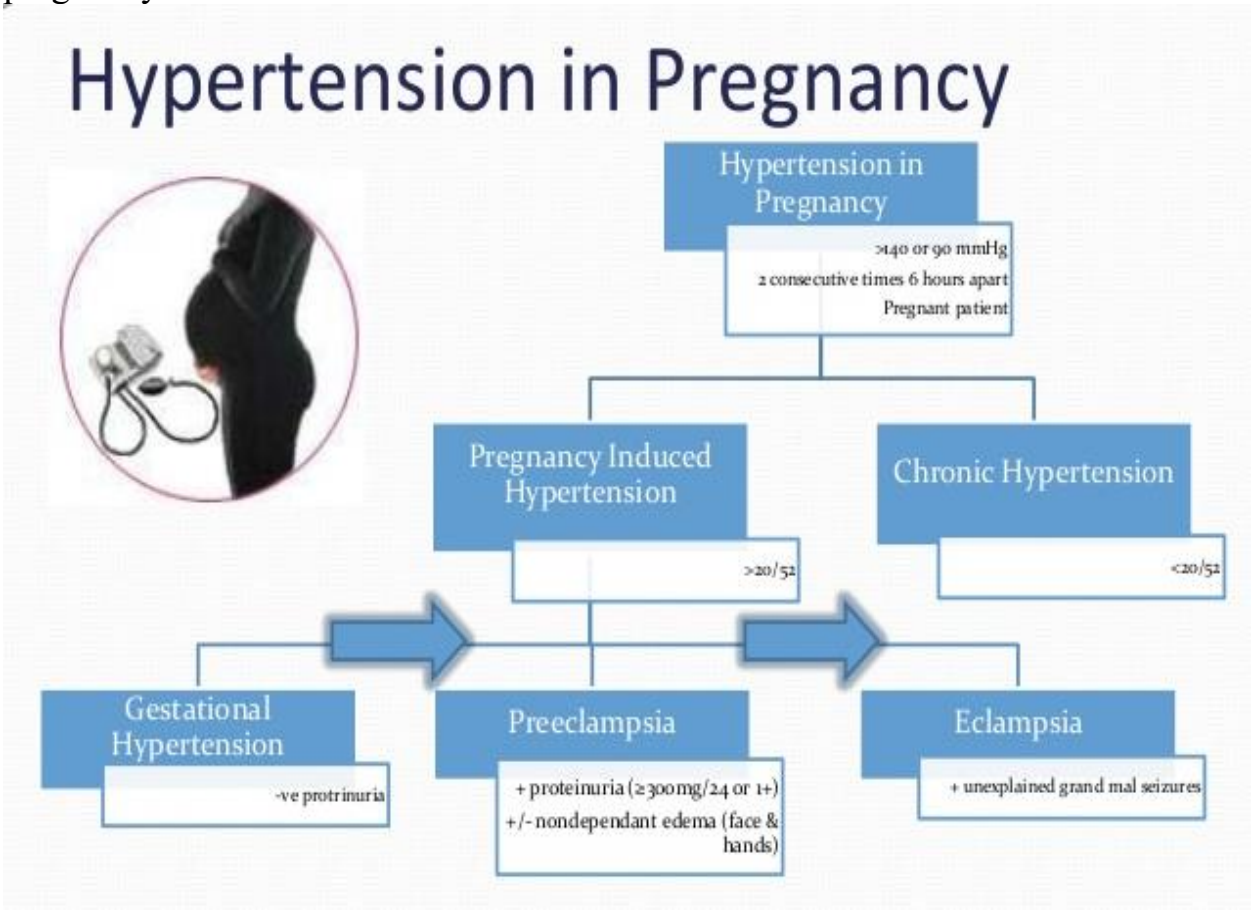
Chorea can also be a manifestation of drug toxicity (for example, anticonvulsants, antiparkinson agents, neuroleptics, steroids, and estrogen), or a result of an

infectious disease such as meningovascular syphilis, Lyme disease, viral encephalitis, and many others.
Drug treatment is indicated for patients with severe disabling chorea. It is treated with haloperidol, chlorpromazine alone or in combination with diazepam, and also pimozide, which is another neuroleptic drug which may have fewer adverse effects than haloperidol. Valproic acid, chloral hydrate, risperidone, or phenobarbital can also be used. Psychotherapy, massage, and muscle stretching exercises used to relieve symptoms during an attack.
Osteomalacia gravidarum is an extremely rare and predetermined decalcification of bone and soft tissue. Most often affects the bones of the pelvis and spine, which is accompanied by their painless stretching. During the palpation of the pubic symphysis a pregnant woman feels painfulness. On X-ray examination of the pelvis sometimes divergence of the bones of the pubic symphysis is detected, however, despite of real osteomalacia, destructive changes in bones are absent.
Treatment of osteomalacia is to normalize phosphor-calcium metabolism. At the present stage, the entire metabolism of minerals in bones, leading to their resorption, is diagnosed using densitometry - a modern ultrasound method for studying bone. Fish fat, calciferol (vitamin D) and ultraviolet radiation are used.



Prevention of early gestosis
Prevention of early preeclampsia consists in the treatment of chronic extragenital diseases of pregnant women, psychoemotional rest of pregnant women, and reducing the influence of environmental factors.
Pregnant women with early preeclampsia, especially with its recurrence, put at risk obstetric and perinatal pathologies (miscarriage, pregnancy, placental insufficiency, fetal hypotrophy, pathology of the newborn), including the prevention of these complications.
Hypertensive disorders in pregnancy.
Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. Hypertension is a sign of an underlying pathology which may be preexisting or appears for the first time during pregnancy. The identification of this clinical entity and effective management play a significant role in the outcome of pregnancy, both for the mother and the baby. In the developing countries with inadequately cared pregnancy, this entity on many occasions remains undetected till major

complications supervene. In Ukraine, there is different terminology regarding this pathology. Until then, use the term - hypertension, pregnancy, this can be considered obsolete. The modern terms are – preeclampsia, hypertensive disorders of pregnancy.



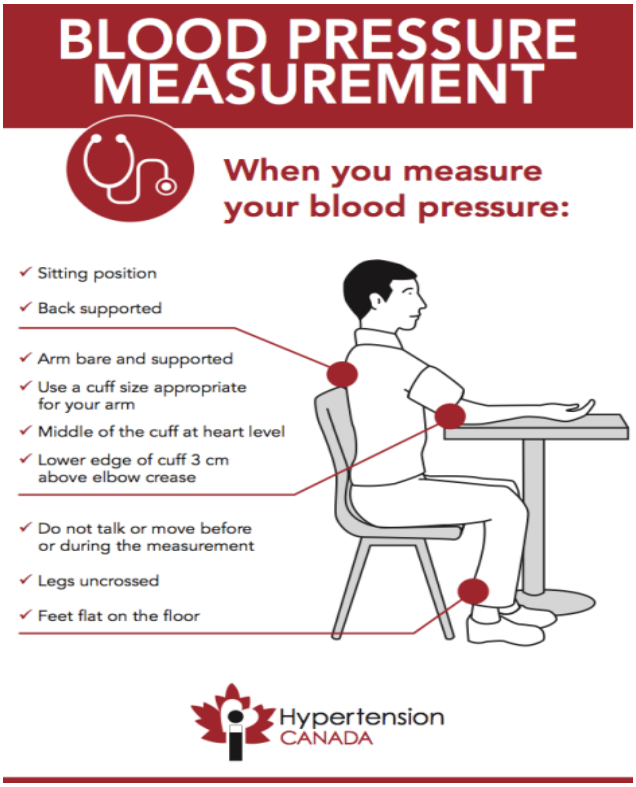
Classification of Hypertension in Pregnancy (National High Blood Pressure Education Program 2000)

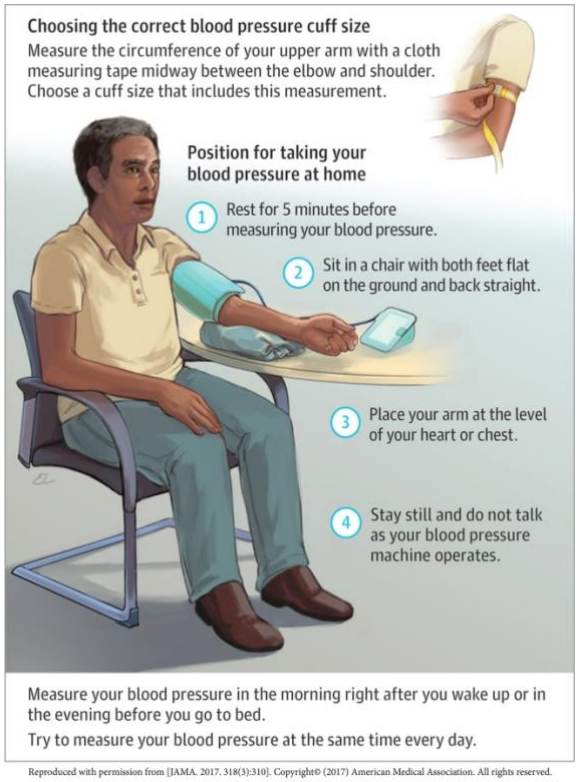
Disorder	Definition	Disorder	Definition
Hypertension	BP ≥ 140/90 mm Hg measured 2 times with at least a 6-hour interval	Chronic hypertension with super imposed preeclampsia and eclampsia	The common causes of chronic hypertension: (a) Essential hypertension (b) Chronic renal disease (reno vascular) (c) Coarctation of aorta (d) Endocrine disorders (diabetes mellitus, pheochromocytoma, thyrotoxicosis (e) Connective tissue diseases (Lupus erythematosus). t The criteria for diagnosis of super imposed pre-eclampsia: (i) New onset of
Proteinuria	Urinary excretion of ≥ 0.3 gm protein/24 hours specimen or 0.1 gm/L		
Gestational hypertension	BP ≥ 140/90 mm Hg for the first time in pregnancy after 20 weeks, without proteinuria		
Pre-eclampsia	Gestational hypertension with proteinuria		

Eclampsia	Women with pre-eclampsia complicated with convulsions and/ or coma	proteinuria >0.5 gm/24 hours specimen. (ii) Aggravation of hypertension. (iii) Thrombocytopenia or (iv) Raise of liver enzymes
Chronic hypertension	Known hypertension before pregnancy or hypertension diagnosed first time before 20 weeks of pregnancy	
Superimposed pre-eclampsia or eclampsia	Occurrence of new onset of proteinuria in women with chronic hypertension	

DC Dutta, Hiralal Konar, 2013

Blood preassure measurement





Treatment

Drug	Dosage	Comments
Labetalol	200–2,400 mg/d orally in two to three divided doses. Commonly initiated at 100–200 mg twice daily	Potential bronchoconstrictive effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.
Nifedipine	30–120 mg/d orally of an extended-release preparation. Commonly initiated at 30–60 mg once daily (extended-release)	Do not use sublingual form. Immediate-release formulation should generally be reserved for control of severe, acutely elevated blood pressures in hospitalized patients. Should be avoided in tachycardia.
Methyldopa	500–3,000 mg/d orally in two to four divided doses. Commonly initiated at 250 mg twice or three times daily	Safety data up to 7 years of age in offspring. May not be as effective as other medications, especially in control of severe hypertension. Use limited by side effect profile (sedation, depression, dizziness).
Hydrochlorothiazide	12.5–50 mg daily	Second-line or third-line agent

Drug	Dose	Comments	Onset of Action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV	Tachycardia is less common and fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5–10 mg/hr	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if needed; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5–10 minutes

ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy

Pre-eclampsia

Pre-eclampsia (PE) is a multisystem disorder of pregnancy previously defined by the onset of hypertension accompanied by significant proteinuria after 20 weeks of gestation. Recently, the definition of PE has been broadened.2–5 PE typically affects 2%–5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early onset.6,7 Globally, 76 000 women and 500 000 babies die each year from this disorder.8 Furthermore, women in low-resource countries are at a higher risk of developing PE compared with those in high-resource countries.

Classification Preeclampsia HIC-10: O13-O15

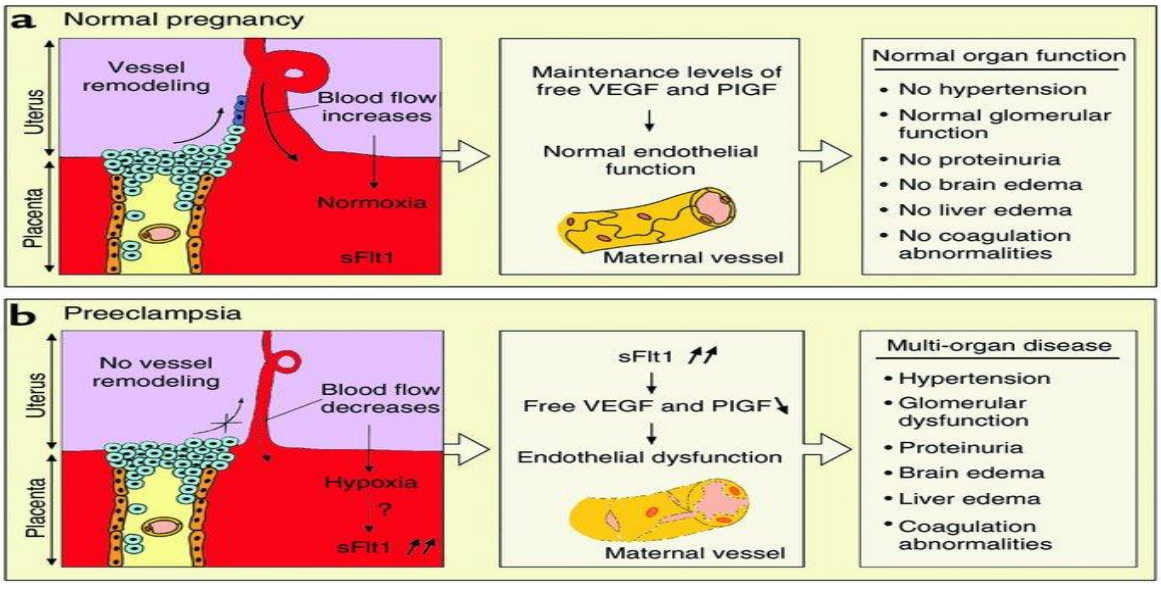
- Light Preeclampsia or gestational hypertension without significant proteinuria
- Preeclampsia moderate
- Heavy Preeclampsia
- Preeclampsia unspecified
- Eclampsia
- Eclampsia during pregnancy
- Eclampsia childbirth

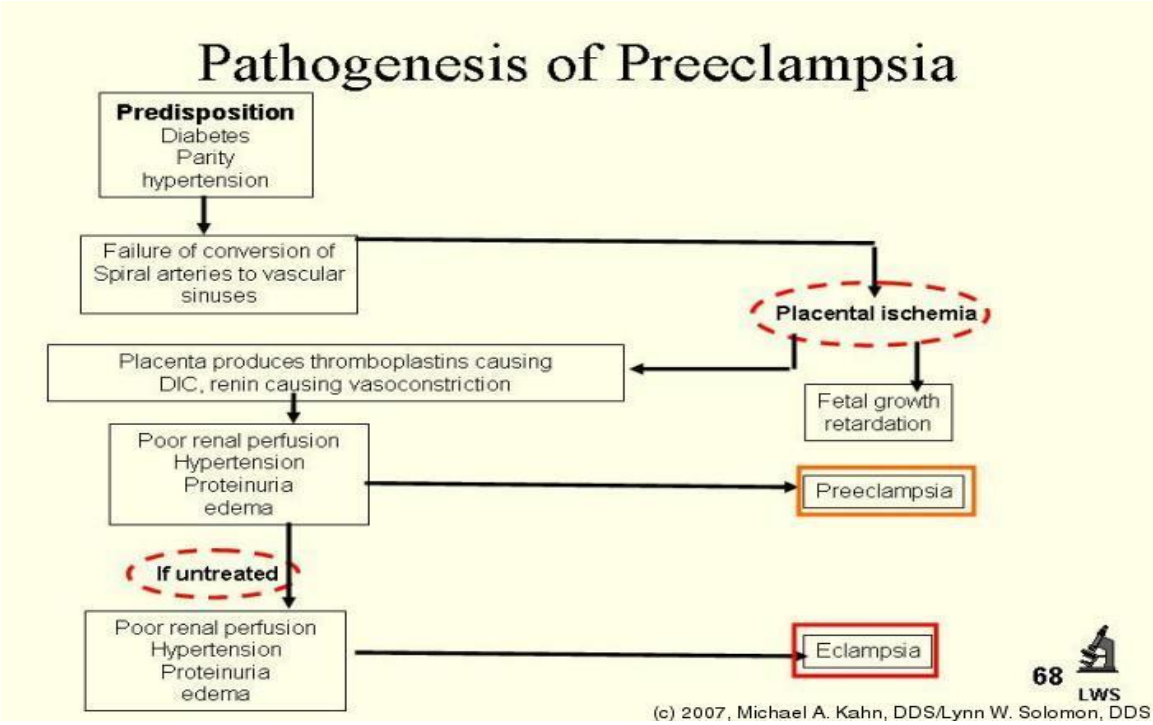
- Eclampsia in the postpartum period
- Eclampsia unspecified for the period
- Etiopatogenesis of Preeclampsia

There are about 30 different theories. Among the causes of preeclampsia, especially severe, the leading place belongs to extragenital, autoimmunological disorders, endocrine diseases. A large number of different theories of the pathogenesis of preeclampsia suggest that none of them fully describes it.

Important role in the origin Preeclampsia belongs to:
1. failure of the spiral arterioles of the uterus, which causes violation of placental blood circulation
2. endothelial dysfunction associated with autoimmunal disorder caused by pregnancy.

Changes in the organs characteristic of preeclampsia:
1. In the cardiovascular system: generalized vasospasm, increased peripheral vascular resistance, hypovolemia.
2. Hematologic changes: Activation of platelets, which is accompanied by consumption coagulopathy, reduced plasma volume, increase blood viscosity, haemoconcentration.
3. In the kidneys: proteinuria, reduced glomerular filtration rate, reduced excretion of uric acid.
4. In the liver: pericortal necrosis, subcapsular hematoma.
5. In CNS: Brain edema, intracranial hemorrhage.





There is a severe form of clinical preeclampsia - HELLP-syndrome (Hemolysis-microangiopathic hemolytic anemia, Elevation of Liver enzymes - increased concentration of liver enzymes in blood plasma, Low platelet count - decreased platelets). Pathophysiological changes in HELLP syndrome occur mainly in the liver. Segmental vasospasm leads to impaired blood flow in the liver and swelling of the Glisson's capsule (pain in the upper abdominal area). Hepatocellular necrosis associated with increased transaminases.

Thrombocytopenia and hemolysis occur as a result of endothelial damage in vascular changes. If this vicious circle of endothelial damage and intravascular activation coagulation should not be interrupted, then WIS syndrome with fatal bleeding develops within a few hours.

Risk factors of preeclampsia:

1. Extragenital pathology: kidney, liver, hypertension, chronic lung and bronchus, heart defects, diabetes mellitus, obesity.
2. Obstetric and gynecologic risk factors:

• presence of hypertensive disorders in family history;
• a previous pre-eclampsia;
• age of the pregnant woman (less than 20, more than 30 years);
• hydramnios, twins;
• anemia of pregnant women;
• isosensibilization for Rh-factor and the ABO-system;

3. Social and domestic factors:

• bad habits;
• occupational hazards;
• unbalanced diet.

Presence of

Hypertension

- SBP ≥ 140 or DBP ≥ 90
- 2 readings 6 hours apart
- > 20/52 gestation

Proteinuria

- ≥ 1+ Urine dipstick (not sensitive)
- ≥ 300 mg / 24

Nondependent Edema

- Hand
- Face
- Not sensitive or specific

Preeclampsia – Risk Factors

Immunogenic Related

- Nulliparous
- Previous preeclampsia
- Multiple Gestation
- Abnormal Placentation

Disease Related

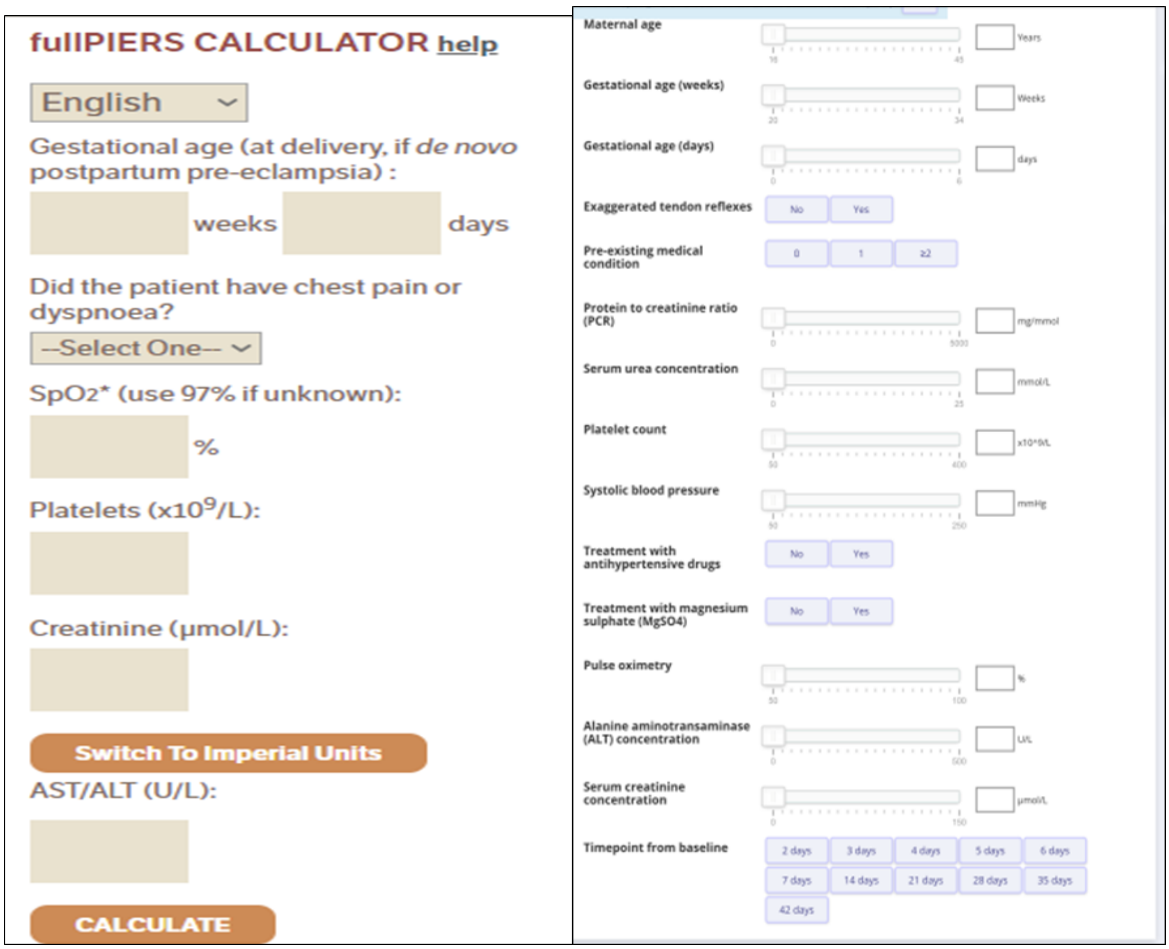
- Chronic HTN
- Chronic Renal Disease
- Collagen Vascular Disease
- Pregestational DM

Maternal Related

- African American
- Obesity
- 35 < Age < 20
- New paternity
- Cohabiliation < 1 year

Family History

- Relatives
- Mother-in-Law



Knowledge of risk factors of preeclampsia and allow for timely detection of risk groups on the occurrence of preeclampsia.

Clinical manifestations

The classic triad of preeclampsia symptoms (edema, proteinuria, hypertension), described in 1913 by the German obstetrician Zangemeister.

Headache, blurred vision, pain in the epigastrium and right hypogastric area are clinical manifestations of severe preeclampsia.

Diagnosis

Diagnosis of preeclampsia at gestational age more than 20 weeks in the presence of blood pressure more than 140/90 mm hg or with an increase in diastolic blood pressure by 15% of the initial in the first trimester of pregnancy in the presence of proteinuria (protein in daily urine more than 0.3 g / l) and general edema (an increase in the body weight of a pregnant woman more than 900.0 g per week, or 3 kg per month). The diagnosis of preeclampsia determines the presence of hypertension and proteinuria or general edema or the presence of all three signs.

Diagnostic criteria of severe preeclampsia / eclampsia.

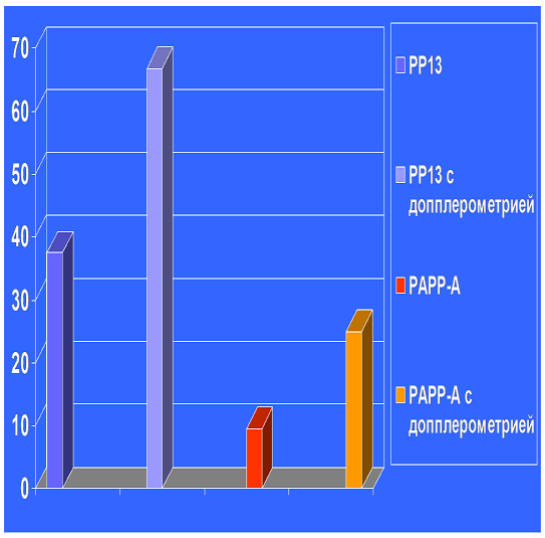
Diagnosis	Diast. BP mm. hg	Proteinuria g / ext	Other signs

Gestational hypertension or mild preeclampsia	90-99	<0,3	-
Preeclampsia moderate	100-109	0,3-5,0	Swelling in the face, hands Sometimes a headache
Severe preeclampsia	≥110	>5	Swelling generalize, significant Headache Dysopia Pain in the epigastrium and / or right hypochondrium Hyperreflexia Oliguria (<500 ml / ext) Thrombocytopenia
Eclampsia	≥90	≥0,3	Convulsive attack (one or more)

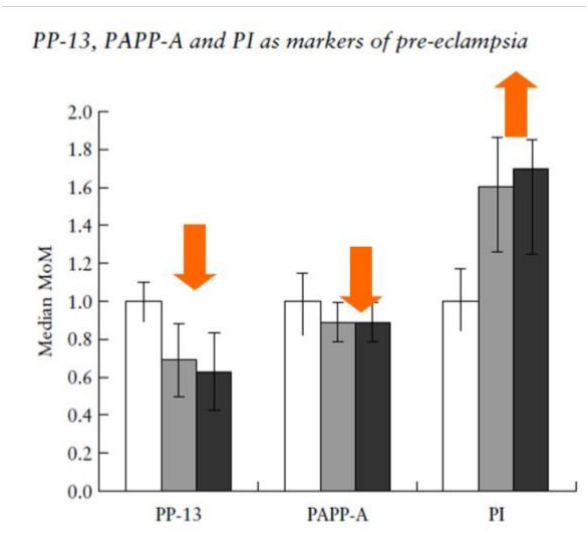
NB! Available in a pregnant woman at least one of the criteria for more severe preeclampsia is the basis for a diagnosis.
At this time there is «pure» and «complicated» form of preeclampsia. Complicated preeclampsia develops on the background of extragenital diseases.
!!!!! As a criterion for severity!!! examination of hypertension in pregnancy, indications for the beginning of antihypertensive treatment and evaluate its effectiveness using only the value diastolic BP. To determine the latter should take into account V Korotkov's tone (but not IV, as before).
To diagnose preeclampsia also need to identify additional clinical and laboratory criteria (Table.2). Additional clinical and laboratory criteria of preeclampsia

Signs of preeclampsia	Light	Moderately	Heavy
Uric acid, mlmol / l	<0,35	0,35-0,45	> 0,45
Urea, mlmol / l	<4,5	4,5-8,0	> 8
Creatinine, Umol / l	<75	75-120	> 120 or oliguria
x 109 platelets / l	> 150	80-150	<80

Prognostic significance

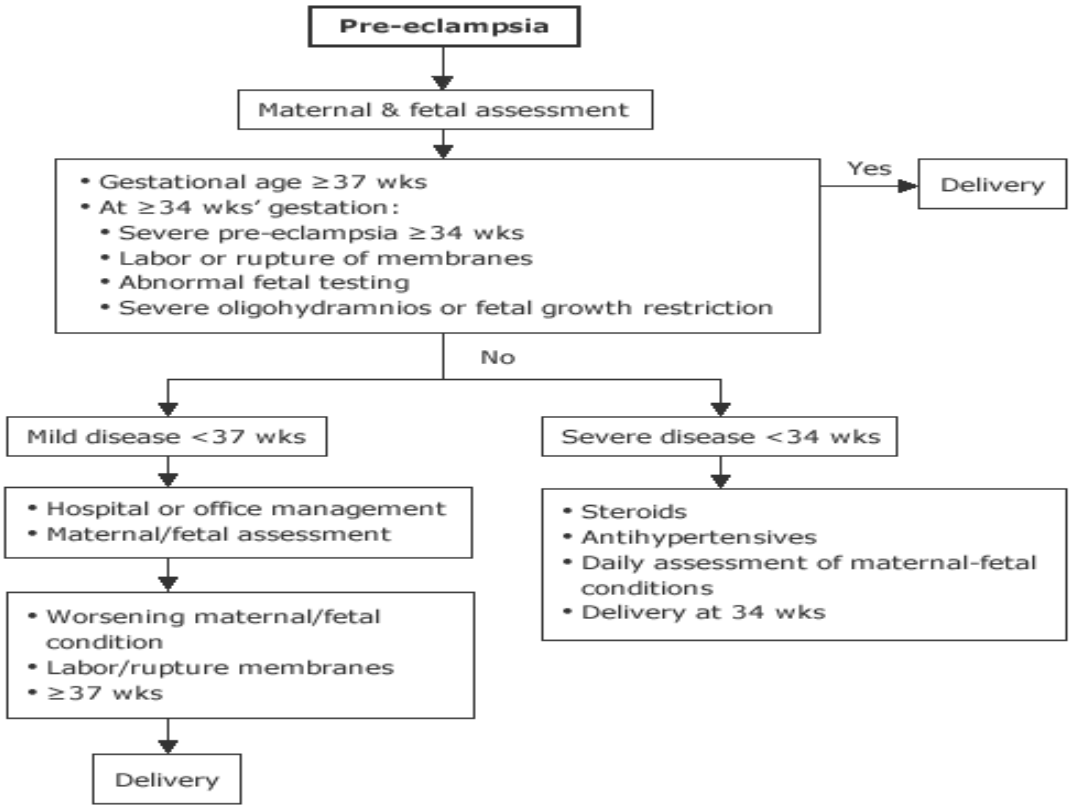


Khalil A., 2010 ., Odibo A.O.,2011



Spencer K. 2007

Treatment of Preeclampsia



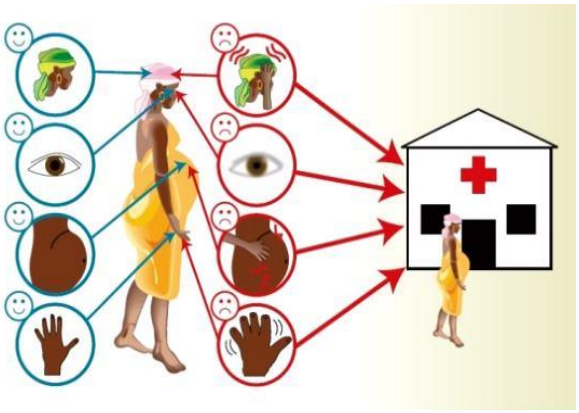
Provision of assistance depends on the pregnant woman, the parameters of BP and proteinuria.

Mild Preeclampsia

In the case of the pregnant woman match the criteria for mild Preeclampsia of pregnancy before 37 weeks of possible care in a hospital day stay. Conduct research:

measuring blood pressure, monitoring fluid balance and edema, checking fetal movements.
Conduct laboratory tests: general urine analysis, daily proteinuria, plasma creatinine and urea, hemoglobin, hematocrit, platelet count, coagulogram, ALT and AST, fetal determination (if possible, not a stress test). Drug therapy is not indicated. Do not limit your intake of liquids and table salt.
Indications for hospitalization
The appearance of at least one sign of moderate preeclampsia; fetal hypoxia.
In the case of a stable state of women within the criteria of light preeclampsia tactics of pregnancy expectant. Delivery – per vias naturalis.

Moderate Preeclampsia
Hospitalization of a pregnant woman in a hospital. Initial laboratory tests: complete blood count, hematocrit, platelet count, coagulogram, ALT and AST, blood group and Rh factor (in the absence of accurate information), general urinalysis, determination of daily proteinuria, creatinine, urea, uric acid, plasma electrolytes (sodium and potassium), fetal health assessment.
Protective regime - limitation of physical and mental stress.



Nutrition: High-protein food, no salt and water restrictions, and non-thirsty foods.
A complex of vitamins and minerals for pregnant women, if necessary, an iron supplement. When diastolic BP> 100 mm Hg Appointment of antihypertensive drugs (metildopa of 0,25-0,5 g 3-4 times a day, maximum dose - 3 g per day, and if necessary add nifedipine 10 mg 2-3 times a day, maximum daily dose - 100 mg).
In term pregnancy before 34 weeks of prescribed corticosteroids for prevention of respiratory distress syndrome (RDS) - dexamethasone 6 mg every 12 hours, four times over 2 days.
Research is carried out with a fixed multiplicity of dynamic monitoring indicators:
- blood pressure control - every 6 hours on the first day, then - twice a day;
- auscultation of the fetal heart every 8 hours;
- urine - daily;
- daily proteinuria
- hemoglobin, hematocrit, coagulogram, platelet count, ALT and AST, creatinine Urea - every three days;
- Daily monitoring of fetus

In progress of preeclampsia begin preparations for delivery:

Delivery.

Progression of preeclampsia or deterioration of fetal state - begin preparations for delivery:

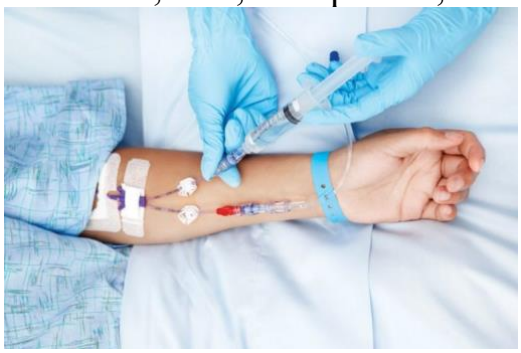
- in the case of "immature" cervix - prostaglandin E2 (locally).
- not effective – Cesearian section
- "mature" cervix – stimulation of patrimonal activity and delivery per vias naturalis.

Go to the conduct of pregnant for heavy preeclampsia algorithm is performed in cases of increase of at least one of the following:

• diastolic BP> 110 mm Hg.;
• headache;
• visual impairment;
• pain in the epigastric area and right hypogastric;
• signs of liver failure;
• oliguria (<25 ml / year);
• thrombocytopenia (<100 • 109 / L);
• Signs of WIS-syndrome;
• Enhancement of ALT and AST.

Sever Preeclampsia

The pregnant woman is admitted to the Anesthesiology Unit and Intensive Care Unit Level III to assess the maternal and fetal risk of pregnancy and select a delivery method within 24 hours. Allocate an individual ward for round-the-clock supervision of medical personnel. Immediate consultation by therapists, neurologist, ophthalmologist. Catheterization of peripheral veins. Initial laboratory tests: complete blood count, hematocrit, platelet count, coagulogram, ALT and AST, blood group and Rh factor (if not), total urine, determination of proteinuria, creatinine, urea, total protein, bilirubin and its fractions, electrolytes.



Careful observation of the dynamic:

• Blood pressure control - every hour;
• Urine test - every 4 hours;
• Monitoring of hourly urine output (bladder catheterization)
• Hemoglobin, hematocrit, platelet count, liver function tests, plasma creatinine - every day;
• Auscultation of the fetal heart - every 15 minutes;

- Monitoring of the fetus: the number of movements in 1 hour, heart rate - every day, if possible - Doppler monitoring of blood circulation in the vessels of the umbilical cord, vessels of the fetal brain, placenta and fetoplacental complex;

- Assessment of amniotic fluid and fetal biophysical profile;
- Cardiotocography

Treatment.

Conservative treatment (severe hospital beds). In term of pregnancy to 34 weeks - corticosteroids for the prevention of RDS-dexamethasone 6 mg every 12 hours, four times, for 2 days. The tactics is active with delivery in the next 24 hours from the moment of diagnosis, regardless of the gestational age.

Antihypertensive therapy.

Treatment of hypertension is not pathogenic, but necessary for the mother and fetus. Lowering systolic pressure is intended to prevent hypertensive encephalopathy and cerebral hemorrhage. It should seek to bring the systolic pressure to a safe level (150 / 90-160 / 100 mm Hg, Not lower!), Ensure the maintenance of adequate cerebral and placental blood flow. Antihypertensive therapy is performed with an elevated diastolic pressure> 100 mm Hg. It has been proven that pharmaceutical antihypertensive therapy should not be started if blood pressure is <150/100 mm Hg. Lowering blood pressure with drug therapy can improve the effects of pregnancy on the mother, but not on the fetus. Of the antihypertensive drugs used during pregnancy: Methyldopa 1.0-3.0 g per day (drug of choice), nifedipine 5-10 mg sublingually, labetalol 10 mg intravenously, blockers, clonidine 0.5-1 ml 0.01%. solution intravenously or intramuscularly, or 0.15-0.2 mg under the tongue 4-6 times a day, hydralazine 20 mg (1 ml) intravenously, if it is possible to study the type of hemodynamics, antihypertensive therapy is carried out for its purpose. In the case of hypersynetics, it is advisable to use a combination of labetalol with nifedipine, in the case of hypocinetic - clonidine, nifedipine against the renewal of the BCC, with eucinetic – methyldopa and nifedipine.

The use of diuretics should be avoided, especially in cases of preeclampsia (with the exception of pulmonary edema or renal failure). Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are absolutely contraindicated.

How do anticonvulsants work with the antihypertensive effects of magnesium sulfate, which is the drug of choice for the prevention and treatment of seizures that occur in hospitalized women as a result of inadequate treatment of severe preeclampsia.

It is absolutely proven that magnesium sulfate prevents the development of eclampsia and is the drug of choice for its treatment. All women with eclampsia should receive magnesium sulfate during labor and within 24 hours after birth. Magnesium sulfate therapy - bolus of 4 g dry weight of magnesium sulfate (w / w 5 minutes) followed by continuous intravenous infusion at a rate determined by the patient. Magnesium sulfate therapy is started from the moment of hospitalization if the diastolic blood pressure is> 130 mm Hg. The appointment of magnesium sulfate therapy is to maintain the concentration of magnesium ions in the blood of pregnant women at the level necessary to prevent seizures.

Signs of magnesium intoxication are possible even against the background of therapeutic plasma concentrations of magnesium, provided that it is combined with other drugs, especially calcium channel blockers. When signs of magnesium sulfate

toxicity appear, 1 g of calcium gluconate (10 ml of a 10% solution) intravenously is prescribed, which should always be at the patient's bedside.
Monitoring a pregnant woman during antihypertensive therapy and magnesium sulfate therapy includes measuring blood pressure every 20 minutes, monitoring the heart rate, frequency and breathing pattern (at least 14 in 1 minute). Determination of O2 saturation (not less than 95%); ECG, check of knee reflexes every 2 hours, control of urine output (at least 50 ml / hour). In addition, control symptoms severity increased preeclampsia: headache, visual impairment (double vision, "flickering flies" in the eyes), epigastric pain, symptoms of possible pulmonary edema (chest tightness, cough, suffocating fever, increased CVP, appearance of crepitus or wet rales on auscultation), increased heart rate and signs of hypoxia, decreased level of fetal consciousness (auscultation of the heart hourly, fetal monitoring).
Fluid management.
A prerequisite for adequate fluid therapy is strict control of volume, fluid and diuresis. Diuresis should be at least 50 ml / h. The total volume of injected fluid should satisfy the daily physiological needs of the woman (on average 30-35 ml / kg) with the addition of volumetric non-physiological costs (blood loss, etc.). The rate of fluid introduction should not exceed 85 ml / hour, or diuresis 30 ml / hour. The drugs of choice for infusion therapy at the time of delivery are isotonic solution (Ringer, NaCl 0.9%). If it is necessary to resume the BCC, the optimal therapy is 6% or 10% solutions of hydroxyethyl starch (Stabizol, Refortan). Hydroxyethyl starch or dextran should be injected with crystalloid in a ratio of 2: 1. It is advisable to include donor fresh frozen plasma in the infusion-transfusion program to eliminate hypoproteinemia (plasma protein values <55 g / l), normalize the anticoagulant / procoagulants, which is the prevention of bleeding during delivery and in the postpartum period.
Do not use hypoosmotic solutions - 5% and 10% glucose and their mixtures with electrolytes (polarization mixture), because they often cause hypoglycemia in the fetus and increase the accumulation of lactate in the mother's brain, worsen the neurological prognosis in case of eclampsia. Before the administration of glucose solutions, a patient with severe preeclampsia succeeds only according to absolute indications - hypoglycemia, hypernatremia and hypertensive dehydration, sometimes - in patients with diabetes mellitus to prevent hypoglycemia.
Tactics of delivery.
Delivery conducted with a view of obstetric situation. Preference is given to vaginal delivery with adequate anesthesia (epidural or nitrous oxide inhalation). Provided ready to spend maternity ways amniotomy with induction of labor with oxytocin.
With an unprepared cervix and the absence of the effect of the drug, prostaglandin is prescribed, or in case of progression of hypertension, the threat of a convulsive seizure, deterioration of the condition, a cesarean section is performed.
The indication for elective cesarean section in cases of severe preeclampsia is the progression of preeclampsia or deterioration of the fetus in pregnant women with premature birth.

If the condition of a pregnant woman or a fetus worsens in the second stage of labor, forceps are applied or vacuum extraction of the fetus is performed against the background of adequate anesthesia.
In the third stage of labor - uterotonic therapy to prevent bleeding (intravenous oxytocin). Metilergometine not apply!
After starting treatment, preeclampsia continues depending on the woman's condition, clinical symptoms and laboratory parameters. Blood pressure control and antihypertensive therapy are required. Doses of antihypertensive drugs are gradually reduced, but not earlier than 48 hours after delivery. Magnesium sulfate therapy lasts at least 24 hours after birth.

Preeclampsia postpartum

Assign a protective mode, blood pressure control, balanced diet. Laboratory examination: General blood test (hemoglobin, hematocrit, platelet count) and urine, biochemical blood test (ALT and AST, bilirubin, creatinine, urea, total protein), coagulogram.
Treatment. Provided that antihypertensive drugs are used during delivery, their administration is continued in the postpartum period. In case of insufficient effectiveness of therapy, thiazide diuretics are added. If this is your first time postpartum hypertension, start treatment with a thiazide diuretic. Magnesium sulfate is prescribed for indications in case of risk of eclampsia. They closely monitor uterine involution. Prevention of bleeding with oxytocin.

Eclampsia

The term eclampsia is derived from a Greek word, meaning “like a flash of lightening”. It may occur quite abruptly, without any warning manifestations. In majority (over 80%); however, the disease is preceded by features of severe pre-eclampsia
The high risk of developing eclampsia suggest: Severe headache, high hypertension (diastolic BP > 120 mm Hg), nausea, pukes, blurred vision, pain in the right hypogastric and or epigastric site.
The main objectives of emergency:
• cessation of seizures;
• renewal of the entrance of the respiratory tract.
Problems of intensive care after the elimination of seizures:
• prevention of recurrent convulsive attacks;
• elimination of hypoxia and acidosis (respiratory and metabolic);
• Prevention of aspiration syndrome;
• Emergency delivery.
Eclamptic convulsion or fit: The fits are epileptiform and consist of four stages
— Premonitory stage: The patient becomes unconscious. There is twitching of the muscles of the face, tongue, and limbs. Eyeballs roll or are turned to one side and become fixed. This stage lasts for about 30 seconds.
— Tonic stage: The whole body goes into a tonic spasm — the trunk-opisthotonus, limbs are flexed and hands clenched. Respiration ceases and the tongue protrudes between the teeth. Cyanosis appears. Eyeballs become fixed. This stage lasts for about 30 seconds.

— Clonic stage: All the voluntary muscles undergo alternate contraction and relaxation. The twitchings start in the face then involve one side of the extremities and ultimately the whole body is involved in the convulsion. Biting of the tongue occurs. Breathing is stertorous and blood stained frothy secretions fill the mouth; cyanosis gradually disappears. This stage lasts for 1–4 minutes.
— Stage of coma: Following the fit, the patient passes on to the stage of coma. It may last for a brief period or in others deep coma persists till another convulsion. On occasion, the patient appears to be in a confused state following the fit and fails to remember the happenings. Rarely, the coma occurs without prior convulsion.

First aid for an attack of eclampsia.

In the event of a seizure attack, treatment begins on the spot. Deploy Intensive Care Unit or to the separation of hospitalized pregnant anesthesiology and intensive care. Put the patient on a flat surface, quickly release the airways, open the mouth and push the lower jaw forward, evacuate the contents of the oral cavity. If possible, if maintained spontaneous breathing, introduced airtransfer and carry oxygen inhalation. With the development of lingering apnea, mechanical ventilation is immediately started through a nasal mask with 100% oxygen supply in the mode of positive pressure at the end of expiration. If convulsions recur or the patient remains in a coma, muscle relaxants are administered and the patient is transferred to artificial ventilation (ALV) and moderate hyperventilation. Artificial lung ventilation (ALV) is not the main method of treating eclampsia, but the elimination of hypoxia (an important pathogenetic factor in the development of multiple organ failure) is a necessary condition for other measures.

With complete recovery of consciousness, the absence of seizures, anticonvulsants are not used, hemodynamic stabilization, stability of the hemostasis system, restoration of the oxygen capacity of the blood (hemoglobin 80 g / l) is followed by a planned cessation of mechanical ventilation, which should be accompanied by a complete cancellation of sedative therapy.

In the case of a cerebral hemorrhage and a coma of a pregnant woman, mechanical ventilation is canceled not earlier than two days later. Continue intensive care in full.

Peripheral vein catheterization is performed and the administration of anticonvulsants (magnesium sulfate - 4 g bolus for 5 minutes intravenously, then maintenance therapy 1-2 g / year) is started under close blood pressure control. Catheterization of bladder. All manipulations (catheterization of veins, urinary bladder, obstetric manipulations) are performed under general anesthesia. After elimination of seizures, metabolic disorders, water-electrolyte balance and acid-base status, and protein metabolism are corrected. Conduct an examination by a neurologist and ophthalmologist. Laboratory tests: complete blood count (thrombocytes, hematocrit, hemoglobin, clotting time), total protein, albumin, glucose, urea, creatinine, transaminases, electrolytes, calcium, magnesium, fibrinogen and its breakdown products, prothrombin time and index, total urinalysis, daily proteinuria.

Delivery is carried out urgently. If the obstetric situation does not allow immediate birth through the vaginal birth canal, perform a caesarean section. Delivery

immediately after the elimination of the seizure attack with the constant administration of magnesium sulfate and antihypertensive therapy. With continued seizures, urgent labor is carried out after the transfer of the patient to mechanical ventilation. Mechanical ventilation continues to stabilize the patient's condition after surgery. After delivery, treatment continues according to the postpartum condition. Magnesium sulfate therapy should be continued for at least 48 hours.

Observation of a woman who suffered preeclampsia / eclampsia after issuing from the maternity hospital. In an antenatal clinic with an outpatient care therapist, a woman who has had moderate to severe preeclampsia or eclampsia:

• nursing home,
• consultation of specialized professionals (if necessary)
• comprehensive examination 6 weeks after delivery

Women who need treatment with antihypertensive drugs after discharge from the maternity hospital undergo weekly examination with mandatory laboratory monitoring of the level of proteinuria and the concentration of creatinine in the blood plasma.

If arterial hypertension persists for 3 weeks after delivery, the woman is hospitalized in a hospital. The duration of outpatient treatment after moderate to severe preeclampsia or eclampsia is 1 year.

The volume and timing of the survey:

• general urine test - 1, 3, 6, 9 and 12 months after birth;
• complete blood count - after 1 and 3 months;
• ophthalmoscopy - 1, 3 and 12 months;
• ECG - after 1 month, then - to appoint a therapist;

It is recommended for women who have undergone preeclampsia, daily monitoring of blood pressure for a year after childbirth. Women who have had gestational hypertension or preeclampsia are at increased risk of developing hypertension in the future; death from stroke, death from all cardiovascular causes..

Therefore, such postpartum should be carried out under the supervision of a doctor and regularly undergo screening (determination of cholesterol and glucose annually).

A psychologist is of great importance for a woman who has undergone eclampsia (as well as for her man), since severe complications of pregnancy often lead to post-traumatic stress disorder.

Prevention of preeclampsia and eclampsia.

Effective prevention Preeclampsia, which have proven efficacy, there is the use antiagrigant therapy and calcium intake.

Annals of Internal Medicine | CLINICAL GUIDELINE

Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: U.S. Preventive Services Task Force Recommendation Statement

Michael L. LeFevre, MD, MSPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 1996 U.S. Preventive Services Task Force (USPSTF) recommendation on aspirin prophylaxis in pregnancy.

Methods: The USPSTF reviewed the evidence on the effectiveness of low-dose aspirin in preventing preeclampsia in women at increased risk and in decreasing adverse maternal and perinatal health outcomes, and assessed the maternal and fetal harms of low-dose aspirin during pregnancy.

Population: This recommendation applies to asymptomatic pregnant women who are at increased risk for preeclampsia and who have no prior adverse effects with or contraindications to low-dose aspirin.

Recommendation: The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation)

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For author affiliation, see end of text.

* For a list of USPSTF members, see the **Appendix** (available at www.annals.org).

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Michael L. LeFevre, MD,MSPH.-2014

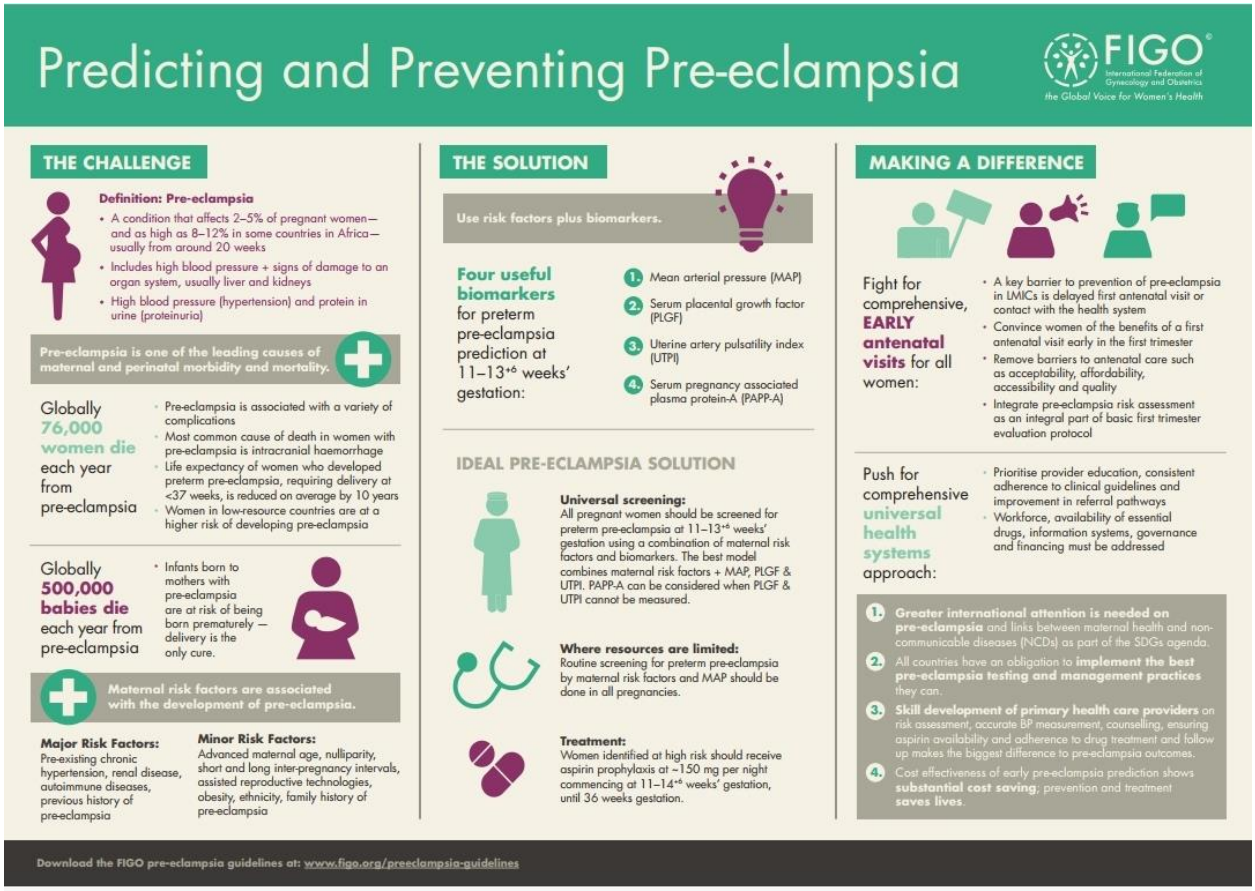
The American Congress of Obstetricians and Gynecologists recommends initiating use of low-dose aspirin (60 to 80 mg/d) during the late first trimester to prevent preeclampsia in women with a medical history of early-onset preeclampsia and preterm delivery (<34 weeks) or history of preeclampsia in more than 1 previous pregnancy

The World Health Organization recommends the use of low-dose aspirin (75 mg/d) starting as early as 12 to 20 weeks of gestation for high-risk women (i.e., those with a history of preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multifetal pregnancies). It states that there is limited evidence regarding the benefits of low-dose aspirin in other subgroups of high-risk women.

The National Institute for Health and Care Excellence recommends that women at high risk for preeclampsia (i.e., those with a history of hypertension in a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or 2 diabetes, or chronic hypertension) take 75 mg/d of aspirin from 12 weeks until delivery. It recommends the same for women with more than 1 moderate-risk factor (first pregnancy, age ≥40 years, pregnancy interval >10 years, body mass index ≥35 kg/m2, family history of preeclampsia, or multifetal pregnancies)

The American Heart Association and the American Stroke Association recommend that women with chronic primary or secondary hypertension or previous pregnancy-related hypertension take low-dose aspirin from 12 weeks until delivery

The American Academy of Family Physicians recommends low-dose aspirin (81 mg/d) after 12 weeks of gestation in women who are at high risk for preeclampsia



Drugs recommended for treatment Preeclampsia

Table 3 Listed drugs approved for treatment Preeclampsia.

Drug	Dosage	Comments
Labetalol	200–2,400 mg/d orally in two to three divided doses. Commonly initiated at 100–200 mg twice daily	Potential bronchoconstrictive effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.
Nifedipine	30–120 mg/d orally of an extended-release preparation. Commonly initiated at 30–60 mg once daily (extended-release)	Do not use sublingual form. Immediate-release formulation should generally be reserved for control of severe, acutely elevated blood pressures in hospitalized patients. Should be avoided in tachycardia.
Methyldopa	500–3,000 mg/d orally in two to four divided doses. Commonly initiated at 250 mg twice or three times daily	Safety data up to 7 years of age in offspring. May not be as effective as other medications, especially in control of severe hypertension. Use limited by side effect profile (sedation, depression, dizziness).
Hydrochlorothiazide	12.5–50 mg daily	Second-line or third-line agent

Drug	Dose	Comments	Onset of Action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV	Tachycardia is less common and fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5–10 mg/hr	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if needed; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5–10 minutes

International Nonproprietary Name	Trade names
1	2
Acetylsalicylic acid	Aspirin, Aspekard, anopirin, atsesal, Terapin, upsarin etc.
Calcium	Calcium phosphate, calcium gluconate, calcium carbonate, calcium lactate, calcium lactogluconate, calcium glycerophosphate, calcium acetate
Metildofa	Dopegit, aldomet, alfadopa, dopanol
Clonidine	Gemiton, clonidine, katapresan, hlofazolin
Pindolol	Whisky
Oxprenolol	Trazikor
Atenolol	Atenobene, atenova, tenolol, unilok, atenosan, blokatenol, atkardil etc.
Metoprolol	Vazokardin, korvitol, lopresor, metoprolol
Labetalol	Lacardia
Nifedipine	Adalat, corinfar, anifed, kordinin, nicardia, nifebene, nifedikor, Nifecard, farmadinin, fenigidin etc.

Verapamil	Izoptin, finoptinum, lecoptin
Hydralazine (digidralazin)	Apresin
Sodium nitroprusside	Nanipruss
Hydrochlorothiazide	Hypothiazid, gidrotiazid
Furosemide	Lasix, diufur, elsimid, frusemid, Fouronnes
Prazozina	Prazozinbene, polpresin, prazozina
Proroksan	Pyroxene
Preparations of iron II	Gino tardiferon, tardiferon, Sorbifer duruleks, aktiferin, gemofer prolongatum, ferro-gradumet, totem, heferol, ranferon 12 and others.
Dexamethasone	Deksazon, deksaven, fortekortin, dekadron, deksabene

International Nonproprietary Name	Trade names
1	2
Acetylsalicylic acid	Aspirin, Aspekard, anopirin, atsesal, Terapin, upsarin etc.
Calcium	Calcium phosphate, calcium gluconate, calcium carbonate, calcium lactate, calcium lactogluconate, calcium glycerophosphate, calcium acetate
Metildopha	Dopegit, aldomet, alfadopa, dopanol
Clonidine	Gemiton, clonidine, katapresan, hlofazolin
Pindolol	Whisky
Oxprenolol	Trazikor
Atenolol	Atenobene, atenova, tenolol, unilok, atenosan, blokatenol, atkardil etc.
Metoprolol	Vazokardin, korvitol, lopresor, metoprolol

Labetalol	Lacardia
Nifedipine	Adalat, corinfar, anifed, kordinin, nicardia, nifebene, nifedikor, Nifecard, farmadinin, fenigidin etc.
Verapamil	Izoptin, finoptinum, lecoptin
Hydralazine (digidralazin)	Apresin
Sodium nitroprusside	Nanipruss
Hydrochlorothiazide	Hypothiazid, gidrotiazid
Furosemide	Lasix, diufur, elsimid, frusemid, Fouronnes
Prazozina	Prazozinbene, polpresin, prazozina
Proroksan	Pyroxene
Preparations of iron II	Gino tardiferon, tardiferon, Sorbifer duruleks, aktiferin, gemofer prolongatum, ferro-gradumet, totem, heferol, ranferon 12 and others.
Dexamethasone	Deksazon, deksaven, fortekortin, dekadron, deksabene

MATERIALS FOR ACTIVATION OF STUDENTS DURING THE LECTURE: QUESTIONS, SITUATIONAL TASKS, ETC.

QUESTIONS:

- What is the definition of early preeclampsia?
- What is the classification of early preeclampsia?
- What modern views on etiology and pathogenesis of early preeclampsia
- Which clinic vomiting of pregnant?
- What are the methods of examination in early gestosis?
- What are the principles and methods of treatment of vomiting of varying degrees of severity?
- What is the differential diagnosis of different forms of early preeclampsia with other extragenital disease?
- The classification preeclampsia?
- What are the risk factors on the occurrence preeclampsia?
- What are methods of preeclampsia diagnostics?
- Methods of preeclampsia severity evaluation?
- Clinical features and diagnosis of eclampsia?
- Emergency help at attack of eclampsia?
- Obstetrical tactics and treatment of eclampsia?

– Prevention of preeclampsia?

TEST TASKS

Direction: For each of the multiple-choice questions select the lettered answer that is the one best response in each case.

1. A 25 y.o. pregnant woman in her 34th week was taken to the maternity house in grave condition. She complains of headache, visual impairment, nausea. Objectively: solid edema, AP170/130 mm Hg. Suddenly there appeared fibrillary tremor of face muscles, tonic and clonic convulsions, breathing came to a stop. After 1,5 minute the breathing recovered, there appeared some bloody spume from her mouth. In urine: protein - 3,5 g/L. What is the most probable diagnosis?
A. Eclampsia
B. Epilepsy
C. Cerebral hemorrhage
D. Cerebral edema
E. Stomach ulcer
2. A 28 year old parturient complains about headache, vision impairment, psychic inhibition. Objectively: AP200/110 mm Hg, evident edema of legs and anterior abdominal wall. Fetus head is in the area of small pelvis. Fetal heartbeats is clear, rhythmic, 190/min. Internal investigation revealed complete cervical dilatation, fetus head was in the area of small pelvis. What tactics of labor management should be chosen?
A. Forceps operation
B. Cesarean
C. Embryotomy
D. Conservative labor management with episiotomy
E. Stimulation of labor activity
3. A 28-years-old woman complains of nausea and vomiting about 10 times per day. She has been found to have body weight loss and xerodermia. The pulse is 100 bpm. Body temperature is 37, 2oC. Diuresis is low. USI shows 5-6 weeks of pregnancy. What is the most likely diagnosis?
A. Moderate vomiting of pregnancy
B. Mild vomiting of pregnancy
C. I degree preeclampsia
D. Premature abortion
E. Food poisoning
4. A primagravida with pregnancy of 37-38 weeks complains of headache, nausea, pain in epigastrium. Objective: the skin is cyanotic. Face is hydropic, there is short fibrillar twitching of blepharos, muscles of the face and the inferior extremities. The look is fixed. AP200/110 mm Hg; sphygmus of 92 bpm, intense. Respiration rate is 32/min. Heart activity is rhythmical. Appreciable edemata of the inferior extremities are present. Urine is cloudy. What medication should be administered?
A. Droperidolum of 0,25\% - 2,0 ml
B. Dibazolum of 1\% - 6,0 ml
C. Papaverine hydrochloride of 2\% - 4,0 ml

D. Hexenalum of 1\% - 2,0 ml
E. Pentaminum of 5\% - 4,0 m
5. A woman at 30 weeks pregnant has had an attack of eclampsia at home. On admission to the maternity ward AP- 150/100 mm Hg. Predicted fetal weight is 1500 g. There is face and shin pastosity. Urine potein is 0, 66o/oo. Parturient canal is not ready for delivery. An intensive complex therapy has been started. What is the correct tactics of this case management?
A. Delivery by cesarean section
B. Continue therapy and prolong pregnancy for 1-2 weeks
C. Continue therapy and prolong pregnancy for 3-4 weeks
D. Labor induction by intravenous oxytocin or prostaglandins
E. Treat preeclampsia and achieve the delivery by way of conservative management
6. An onset of severe preeclampsia at 16 weeks gestation might be caused by:
A. Hydatidiform mole
B. Anencephaly
C. Twin gestation
D. Maternal renal disease
E. Interventricular defect of the fetus
7. A 25 y.o. pregnant woman in her 34th week was taken to the maternity house in grave condition. She complains of headache, visual impairment, nausea. Objectively: solid edema, BP-170/130 mm Hg. Suddenly there appeared fibrillary tremor of face muscles, tonic and clonic convulsions, breathing came to a stop. After 1,5 minute the breathing recovered, there appeared some bloody spume from her mouth. In urine: protein - 3,5 g/L. What is the most probable diagnosis?
A. Eclampsia
B. Epilepsy
C. Cerebral hemorrhage
D. Cerebral edema
E. Stomach ulcer

8. A 28-years-old woman complains of nausea and vomiting about 10 times per day. She has been found to have body weight loss and xerodermia. The pulse is 100 bpm. Body temperature is 37, 2oC. Diuresis is low. USI shows 5-6 weeks of pregnancy. What is the most likely diagnosis?
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B. Continue therapy and prolong pregnancy for 1-2 weeks
C. Continue therapy and prolong pregnancy for 3-4 weeks
D. Labor induction by intravenous oxytocin or prostaglandins
E. Treat preeclampsia and achieve the delivery by way of conservative management
10. A 19-year-old primigravida woman with a body weight of 54,5 kg gave birth at 38 weeks gestation to a full-term live girl after a normal vaginal delivery. The girl's weight was 2180,0 g, body length - 48 cm. It is known from history that the woman has been a smoker for 8 years, and kept smoking during pregnancy. Pregnancy was complicated by moderate vomiting of pregnancy from 9 to 12 weeks pregnant, edema of pregnancy from 32 to 38 weeks. What is the most likely cause of low birth weight?
A. Fetoplacental insufficiency
B. Low weight of the woman
C. Woman's age
D. First trimester preeclampsia
E. Third trimester preeclampsia
11. A primagravida with pregnancy of 37-38 weeks complains of headache, nausea, pain in epigastrium. Objectively: the skin is cyanotic. Face is hydropic, there is short fibrillar twitching of blepharons, muscles of the face and the inferior extremities. The stare is fixed. BP - 200/110 mm Hg. Respiration rate is 32/min. Heart activity is rhythmical. Appreciable edemas of the inferior extremities are present. Urine is cloudy. What medication should be administered?
A. Droperidolum of 0,25% - 2,0 ml
B. Dibazolum (Bendazole hydrochloride) of 1% - 6,0 ml
C. Papaverine hydrochloride of 2% - 4,0 ml
D. Hexenalum of 1% - 2,0 ml
E. Pentaminum of 5% - 4,0 ml
12. A multigravida on the 38th week of her pregnancy complains of increased BP up to 140/90 mm Hg, edema of the shins for 2 weeks. In the last month she gained 3.5 kg of weight. Urine analysis: protein - 0.033 g/L. Make the diagnosis:
A. Mild preeclampsia
B. Moderate preeclampsia
C. Pregnancy hypertension
D. Severe preeclampsia
E. Pregnancy edema
13. A 35-year-old pregnant woman with degree 1 essential hypertension, developed edemas and headache at the 33 week of her pregnancy. Objectively her general condition is satisfactory, blood pressure - 160/100 mm Mg, normal uterine tone. Fetal heart rate is 140/min., rhythmic. She was diagnosed with daily proteinuria - 4 g/L, daily diuresis – 1100 ml. Creatinine - 120 mcmol/L, urea - 7 mmol/L, platelets - 101 * 10 3/l.. What complication of pregnancy occurred?
A. Mild preeclampsia
B. Hypertensive crisis
C. Moderate preeclampsia
D. Renal failure

E. Severe preeclampsia

Answer key

1	A	8	A
2	A	9	A
3	A	10	A
4	A	11	A
5	A	12	A
6	D	13	C
7	A		

LECTURE 5
"Obstetric bleeding during the second half of pregnancy, childbirth and the postpartum period. Algorithm for providing emergency care for obstetric bleeding"

RELEVANCE: Etiology and pathogenesis, modern diagnostic methods, volumetric survey of patients, clinical features, classification of placenta previa, premature detachment of a normally located placenta and postpartum haemorrhage. are basic to understand here to provide qualified emergency care, modern principles of prevention and medical rehabilitation of the patients. Unless well studied, this can make impossible to master pathological obstetric care and save both mother and child lives.

LEARNING OBJECTIVE is to gain basic knowledge about the etiology, pathogenesis, clinics, diagnostics and treatment of pathological conditions that may cause obstetric haemorrhage. During the course of teaching the material, students develop clinical thinking on this topic, which allows them to further solve problems associated with obstetric haemorrhage. Get knowledge about modern treatment and prevention principles of pregnant women with ante- intra- and postpartum haemorrhage. Develop a special vigilance in the prevention and early diagnosis of obstetrical haemorrhage in students. Form a sense of moral and legal responsibility for the timeliness and quality of medical care obstetric patients.

BASIC CONCEPTS: Pathological conditions which cause obstetrical bleeding. Modern diagnostic methods of placenta previa and premature detachment of a normally located placenta. Clinical signs of placenta previa and premature detachment of a normally located placenta. Classification of placenta previa and premature detachment of a normally located placenta. Principles of pregnant women with placenta previa and premature detachment of a normally located placenta emergency care. Modern principles of placenta previa and premature detachment of a normally located placenta prevention. Causes, pathogenesis, clinics and diagnostics of postpartum haemorrhage. Modern methods of postpartum haemorrhage treatment and prevention. Active management of 3rd stage of labor. Modern methods of blood loss estimation.

EDUCATIONAL MATERIALS

Placenta previa

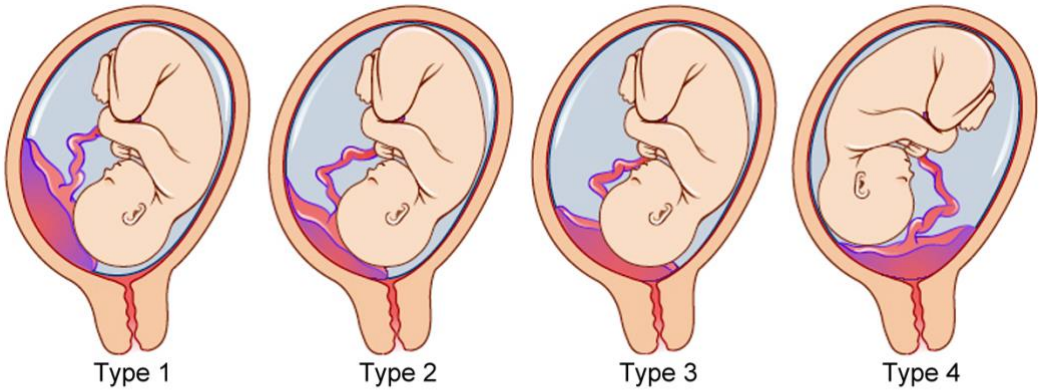
044.0 – Determined placenta previa without bleeding
044.1 – Placenta previa with bleeding

- Placenta previa - pregnancy complication in which placenta is located in the lower uterine segment below the presenting part, blocking all or part of the internal cervical os. During physiological pregnancy, the lower edge of the placenta does not reach any closer than 7 cm to the internal os. Placenta previa is seen in 0,2-0,8 % of all delivers.

Classification of placenta previa

1. Complete presentation - the placenta completely blocks the internal os.
2. Incomplete presentation - the placenta partially blocks the internal os:
   a) Lateral presentation - 2/3 of the area of the internal os is blocked;
   b) Marginal presentation – the edge of the placenta meets the internal os.
3. Low placenta previa (placement) – the placenta is implanted in the lower uterine segment less than 7 cm from the internal os without blocking it.

In connection with migration of the placenta or its growth, the type of presentation can change as the pregnancy continues.



Classifications

Classical	*Contemporary*	*Ultrasound*
Type 1	Marginal	Minor
Type 2	Lateral	
Type 3	Central	Major
Type 4		

ETIOLOGY

The exact cause of implantation of the placenta in the lower segment is not known. The following theories are postulated.

• Dropping down theory: The fertilized ovum drops down and is implanted in the lower segment. Poor decidual reaction in the upper uterine segment may be the cause. Failure of zona pellucida to disappear in time can be a hypothetical possibility. This explains the formation of central placenta previa.

• Persistence of chorionic activity in the decidua capsularis and its subsequent development into capsular placenta which comes in contact with decidua vera of the lower segment can explain the formation of lesser degrees of placenta previa.

• Defective decidua,results in spreading of the chorionic villi over a wide area in the uterine wall to get nourishment. During this process, not only the placenta becomes membranous but encroaches onto the lower segment. Such a placenta previa may invade the underlying decidua or myometrium to cause placenta accreta, increta or percreta

• Big surface area of the placenta as in twins may encroach onto the lower segment.

CAUSE OF BLEEDING: As the placental growth slows down in later months and the lower segment progressively dilates, the inelastic placenta is sheared off the wall

of the lower segment. This leads to opening up of uteroplacental vessels and leads to an episode of bleeding. As it is a physiological phenomenon which leads to the separation of the placenta, the bleeding is said to be inevitable. However, the separation of the placenta may be provoked by trauma including vaginal examination, coital act, external version or during high rupture of the membranes. The blood is almost always maternal, although fetal blood may escape from the torn villi especially when the placenta is separated during trauma.

Clinical symptoms

SYMPTOMS: The only symptom of placenta previa is vaginal bleeding. The classical features of bleeeding in placenta previa are sudden onset, painless, apparently causeless and recurrent. In about 5% cases, it occurs for the first time during labor, especially in primigravidae. In about one-third of cases, there is a history of "warning hemorrhage" which is usually slight. The bleeding is unrelated to activity and often occurs during sleep and the patient becomes frightened on awakening to find herself in a pool of blood. The bleeding is unassociated with pain unless labor starts simultaneously. Obvious causes for the placental separation such as trauma or hypertension are usually absent. However, preeclampsia may complicate a case of placenta previa. The first bout of bleeding is usually not alarming but subsequent bouts may be heavier than the previous one due to separation of fresh areas of placenta. In majority of cases, bleeding occurs before 38 weeks and earlier bleeding is more likely to occur in major degrees. However, there may not be any bleeding in central placenta previa until labor starts. Anemia, as a result of bleeding.

Abdominal examination:

• The size of the uterus is proportionate to the period of gestation. Note the effective reduction of the antero-posterior diameter of the inlet in contrast to type II anterior placenta previa.

• The uterus feels relaxed, soft and elastic without any localized area of tenderness.

• Persistence of malpresentation like breech or transverse or unstable lie is more frequent. There is also increased frequency of twin pregnancy.

• The head is floating in contrast to the period of gestation. Persistent displacement of the fetal head is very suggestive. The head cannot be pushed down into the pelvis.

• Fetal heart sound is usually present, unless there is major separation of the placenta with the patient in exsanguinated condition. Slowing of the fetal heart rate on pressing the head down into the pelvis which soon recovers promptly as the pressure is released is suggestive of the presence of low lying placenta especially of posterior type (Stallworthy's sign). But this sign is not always significant because it may be due to fetal head compression even in an otherwise normal case. Frequently,

incorrect positioning of the fetus occurs: diagonal, transverse, breeched presentation, incorrect insertion of the head. Premature birth is possible.

Diagnostics

1. Anamnesis.

2. Clinical displays - occurrence of repeated bleeding, not accompanied by pain and increased uterus tonus.

Obstetrical examination:

a) External examination:
- High standing of the presented part;
- Diagonal, transverse fetal position;
- The tonus of the uterus is not increased;

b) Internal examination (**performed only in the conditions of an operation room**):
- Doughy tissue in the fornix, swelling, pulsation of vessels;
- Impossible to palpate the presented part through the fornix.

In case of bleeding of specific character, the presentation is not meaningful because the obstetrical tactics are determined by the volume of blood loss and the condition of the woman.

Distinguishing features of placenta previa and abruptio placentae

	Placenta previa	Abruptio placentae
Clinical features: • **Nature of bleeding**	(a) Painless, apparently causeless and recurrent (b) Bleeding is always revealed	(a) Painful, often attributed to preeclampsia or trauma and continuous (b) Revealed, concealed or usually mixed
• **Character of blood**	Bright red	Dark colored
• **General condition and anemia**	Proportionate to visible blood loss	Out of proportion to the visible blood loss in concealed or mixed variety
• **Features of preeclampsia**	Not relevant	Present in one-third cases
Abdominal examination: • **Height of uterus**	Proportionate height to gestational age	May be disproportionately enlarged in concealed type
• **Feel of uterus**	Soft and relaxed	May be tense, tender and rigid
• **Malpresentation**	Malpresentation is common. The head is high floating	Unrelated, the head may be engaged

• **FHS**	Usually present	Placenta in upper segment
Placentography (USG)	Placenta in lower segment	Placenta in upper segment
Vaginal examination	Placenta is felt on the lower segment	Placenta is not felt on lower segment. Blood clots should not be confused with placenta

<u>Placenta previa with bleeding is an urgent indication for hospitalization.</u>

Algorithm of examining a pregnant woman with bleeding in the hospital:

- ➢ Specify the anamnesis;
- ➢ Evaluate the general condition, volume of blood loss;
- ➢ General instrumental tests (blood type, Rhesus factor, general blood analysis, coagulogram);
- ➢ External obstetrical examination;
- ➢ Examination of the uterine cervix and vagina in an operational room with the help of vaginal mirrors to exclude such reasons for bleeding as cervical polyp, cervical cancer, rupture of a varicose node, evaluate vaginal discharge;
- ➢ Additional methods of examination (US) if indicated, if there is no need for urgent delivery.

Treatment:

Treatment tactics depend on the volume of blood loss, conditions of the patient and fetus, character of the presented part, term of the pregnancy, maturity of the fetus's lungs.

Principles for conducting patients with placenta previa:

1. In case of small blood loss (250 ml), absence of symptoms of hemorrhagic shock, fetal distress, absence of labor activity, immaturity of the fetus's lungs before 37 weeks term - waiting tactics.

2. Bleeding that has stopped - US, prepare the fetus's lungs. The purpose of waiting tactics – prolong the pregnancy to term of a viable fetus.

3. In case of progressing uncontrollable bleeding (more than 250 ml), accompanied by symptoms of hemorrhagic shock, fetal distress, regardless of the pregnancy term, condition of the fetus (live, distress, dead) - urgent (emergency) delivery.

Clinical variants:

1. Blood loss (up to 250 ml), there are no symptoms of hemorrhagic shock, fetal distress, term of pregnancy - less than 37 weeks:

- hospitalization;

- tocolytic therapy when indicated;

- quicken the maturing of the fetus's lungs before 34 weeks of pregnancy (dexamethasone 6 mg every 12 hours for 2 days);

- monitoring the woman and fetal condition.

- If bleeding progresses more than 250 ml – delivery by Cesarean section.

2. Considerable blood loss (more than 250 ml) with premature term of pregnancy – regardless of the presented part – emergency Cesarean section.

3. Blood loss (up to 250 ml) with mature pregnancy:

Under the conditions of an operational room, determine the presentation:

- In case of partial placenta previa, intact amniotic sac and cephalic presentation, active uterine contractions, perform amniotomy. If the bleeding stops, delivery can be performed vaginally. After the birth of the baby - i/m introduction 10 units of oxytocin, carefully observe the contractions of the uterus and character of vaginal discharge. If bleeding continues - Cesarean section;

- During complete or incomplete placenta previa, wrong fetal position (pelvic, diagonal or transverse) perform a Cesarean section;

- During incomplete placenta previa, dead fetus perform amniotomy, if the bleeding stops – vaginal delivery.

4. Blood loss (more than 250 ml) mature pregnancy regardless of the presentation - emergency Cesarean section.

5. Complete placenta previa: diagnosed by US, without bleeding – hospitalization till mature term for delivery, Cesarean section at 37-38 weeks.

In the early postnatal period - careful supervision of the woman's condition. If the bleeding reoccurs after Cesarean section and the volume of blood loss is more than 1% of body weight - urgent relaparotomy, hysterectomy without the appendages, if necessary – ligation of the internal iliac arteries by an expert.

Compensation for the blood loss, treatment of hemorrhagic shock and DIC - syndrome is performed when indicated.

Premature detachment of a normally located placenta

Code number - 045 Premature detachment (tearing away of the placenta)

045.0 Premature detachment of the placenta with coagulation dysfunction

045.8 Other premature detachment of the placenta

045.9 Premature non-specified detachment of the placenta

Premature detachment of a normally located placenta is the premature pathological detachement from the uterine walls during the pregnancy or during the I - II periods of labor.

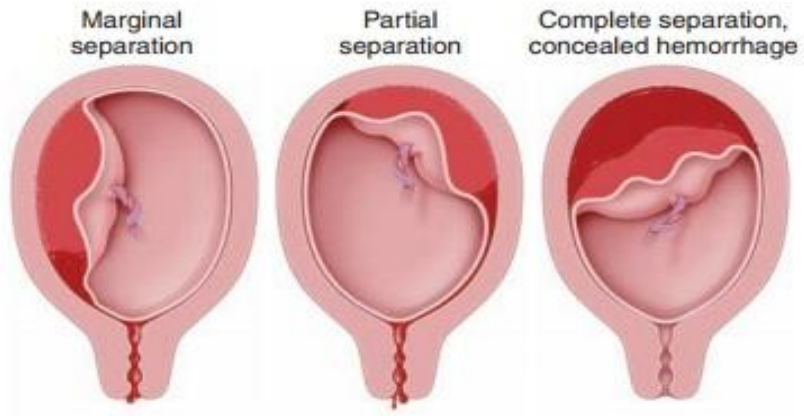


FIGURE 21.3. Types of placental abruption. Note that vaginal bleeding is absent when the hemorrhage is concealed.

ETIOLOGY: The exact cause of separation of a normally situated placenta remains obscure in majority of cases. The prevalence is more with:

- high birth order pregnancies with gravida 5 and above — three times more common than in first birth
- advancing age of the mother
- poor socio-economic condition
- malnutrition
- smoking (vaso-spasm).
- Hypertension in pregnancy is the most important predisposing factor. Pre-eclampsia, gestational hypertension and essential hypertension, all are associated with placental abruption.
- Trauma: Traumatic separation of the placenta usually leads to its marginal separation with escape of blood outside. The trauma may be due to:
    - ➢ Attempted external cephalic version specially under anesthesia using great force
    - ➢ Road traffic accidents or blow on the abdomen
    - ➢ Needle puncture at amniocentesis.

- Sudden uterine decompression: Sudden decompression of the uterus leads to diminished surface area of the uterus adjacent to the placental attachment and results in separation of the placenta. This may occur following—
    - ➢ delivery of the first baby of twins
    - ➢ sudden escape of liquor amnii in hydramnios and
    - ➢ premature rupture of membranes.
- Short cord, either relative or absolute, can bring about placental separation during labor by mechanical pull.
- Supine hypotension syndrome: In this condition which occurs in pregnancy there is passive engorgement of the uterine and placental vessels resulting in rupture and extravasation of the blood.
- Placental anomaly: Circumvallate placenta
- Sick placenta: Poor placentation, evidenced by abnormal uterine artery Doppler waveforms is associated with placental abruption.
- Uterine factor: Placenta implanted over a septum (Septate Uterus) or a submucous fibroid. Torsion of the uterus leads to increased venous pressure and rupture of the veins with separation of the placenta.
- isoimmune conflict between the mother and fetus;
- overdistension of the uterus (hydramnion, multiple pregnancy, large fetus);
- diabetes;
- kidney disease;
- inflammatory processes of the uterus, placenta;

Classification:

1. Complete detachment (the whole placenta detaches).
2. Partial detachment:

- marginal
- central

Clinical symptoms:

1. Pain syndrome: sharp pain at the location of the placenta which then extends to the whole uterus, abdomen, back and becomes diffuse. The pain is most expressed during central detachment and can be not as expressed for marginal detachment. For detachment of a placenta located on the posterior uterine wall, the pain can simulate renal colic.
2. Hypertonus of the uterus up to tetany, which does not decrease with spasmolytic, tocolytic agents.
3. Vaginal bleeding can vary depending on the severity and character (marginal or central) from insignificant to massive. If the hematoma is formed retroplacenta, external bleeding can be absent.

Diagnostics:

1. Condition of the pregnant woman will depend on the size of the detachment, volume of blood loss, occurrences of symptoms of hemorrhagic shock or DIC - syndrome.
2. External obstetrical examination:

- hyper tonus of the uterus;
- the uterus is increased in size, can be deformed with local bulging if the placenta is located on the anterior wall;
- pain, tenderness during palpation;
- difficult or impossible palpation and auscultation of the fetal heart beat;
- occurrence of symptoms of fetal distress or its death.

3. Internal obstetrical examination:
- strained amniotic sac;
- amniotic fluid with blood;
- bleeding of from the uterus.

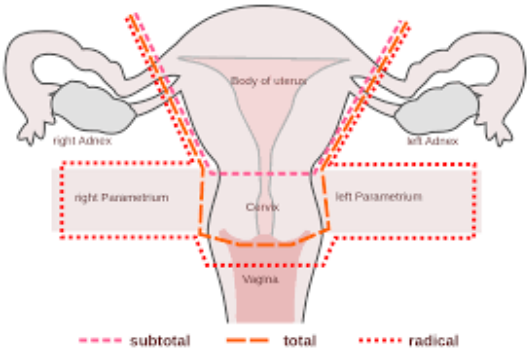
4. US (echo-negative shadow between the uterus and placenta), but this method cannot be absolute diagnostic criterion, because a hypoechogenic zone can be seen in patients without detachments.

In case of absence of external bleeding the diagnosis of premature detachment of placenta is based on increased uterus tonus, local tenderness, deterioration of the fetal condition. Blood from retroplacental hematomas penetrates the wall of the uterus and forms Couvelaire's uterus (utero-placental apoplexy) which then loses the ability to contract, which leads to the development of bleedings with massive blood loss as a result of coagulopathy and hypotonus.

Treatment:

Unreasonably overdue delivery leads to the death of the fetus, development of Couvelaire's uterus, massive blood loss, hemorrhagic shock and DIC - syndrome, loss of reproductive function.

1. In case of progressing premature detachment of the placenta during the pregnancy, or in the first period of labor, with the occurrence of symptoms of hemorrhagic shock, DIC - syndrome, signs of fetal distress, regardless of the pregnancy term - urgent delivery by Cesarean section. In the presence of signs of Couvelaire's uterus – hysterectomy without the uterine appendages.



2. Restore the blood loss, treatment of hemorrhagic shock and DIC - syndrome.

3. In case of non-progressing detachment of the placenta, possible dynamic supervision for premature pregnancy till 34 weeks (carrying out therapy for the maturing of the fetus's lungs), in establishments where there is round-the-clock watch of qualified OBGYN doctors, anesthesiologists, neonatologists. Monitoring of the woman's condition and fetal condition, CTG, US in dynamics are done.

Features of the Cesarean section:

- prior to the operation - amniotomy (if there are conditions);

- obligatory revision of the uterine walls (especially the external surface) for the purpose of an excluding utero-placental apoplexy;

- in case of diagnosing of Couvelaire's uterus - hysterectomy without the uterine appendages;

- if there is a small area of apoplexy - 2-3 foci of small diameter 1-2 cm, or one - up to 3 cm), and the ability of the uterus to contract, absence of bleeding and signs of DIC - syndrome, if necessary to keep reproduction function (first childbirth, dead fetus), there is questions about preserving the uterus. Surgeons observe the condition of the uterus for some time (10-20 min.) with the abdominal cavity still open, in the absence of bleeding the abdominal cavity is drained for hemostasis control. Such tactics, in unusual cases, are performed only in establishments, in which round-the-clock watch of doctors OBGYN, anesthesiologist is available;

- In the early postoperative period - careful supervision of the woman's condition.

Tactics for placental detachment in the end of the I or during the II stages of labor

- Immediate amniotomy, if the amniotic sac is intact;

- If cephalic fetal presentation – apply obstetrical forceps;

- If breech presentation – extraction of the fetus by the pelvic;

- If transverse position of the second twin – perform obstetrical turn with extraction of the fetus by the leg. In some cases more reliable will be Cesarean section;

- Manual detachment of the placenta and removal of the placenta;

- Contractive agents - i/v 10 units of oxytocin, in the absence of effect - 800 mkg misoprostole (rectal);

- Careful dynamic supervision in the postpartum period;

- Restore the blood loss, treatment of hemorrhagic shock and DIC - syndrome.

Reasons for bleeding in the third stage of labor and early postpartum periods (stages):

1. Anomaly of placental abruption processes:

- Insufficient contractility of the myometrium
- Anomalies of placentation
- Strong attachment of the placenta (partial)
- Placenta adherence (partial)
- Ruptured uterus (complete, incomplete)

2. Anomaly in the processes of expulsion of the placenta:

- hypotension of the uterus
- delay of the placenta in the lower segment of the uterus
- incorrect methods of removing the placenta,
- irrational introduction of uterotonics drugs

3. Trauma to the genital tract, in particular the uterus.

4. Placental defects, delay of parts of the placenta, its membranes

5. Hemostasis dysfunction, caused by complicated course of pregnancy and labor (coagulopathy).

Blood loss during labor should be no more than 0,5% of the woman's body weight. This is physiological!

Postpartum bleeding – blood loss more than 0.5% of the woman's body weight after the birth of the baby. Bleedings in some minutes or hours after the delivery - serious and potentially fatal complication. Bleedings can be sudden and profuse, or slow and long.

Classification:
072.0 - Bleeding in the third stage of labor
072.1 - Other bleedings in the early postpartum period
072.2 - Late or secondary postpartum hemorrhage

072.3 - Postpartum coagulation disorder

Types of postpartum hemorrhage:

1. Hemorrhage in the third stage of labor.
2. Primary (early) postpartum hemorrhage which occurs in the early postpartum period or within 24 hours after delivery.
3. Secondary (late) postpartum hemorrhage which occurs after 24 hours and up to 6 weeks after delivery.

Risk factors of postpartum hemorrhage:

- burdened obstetrical anamnesis (bleedings in previous deliveries, abortions, miscarriages);
- preeclampsia;
- big fetus;
- polyhydramnios;
- multiple pregnancy;
- uterus myoma;
- seam on the uterus;
- chronic DIC - syndrome;
- thrombocytopathy;
- antenatal death of the fetus.

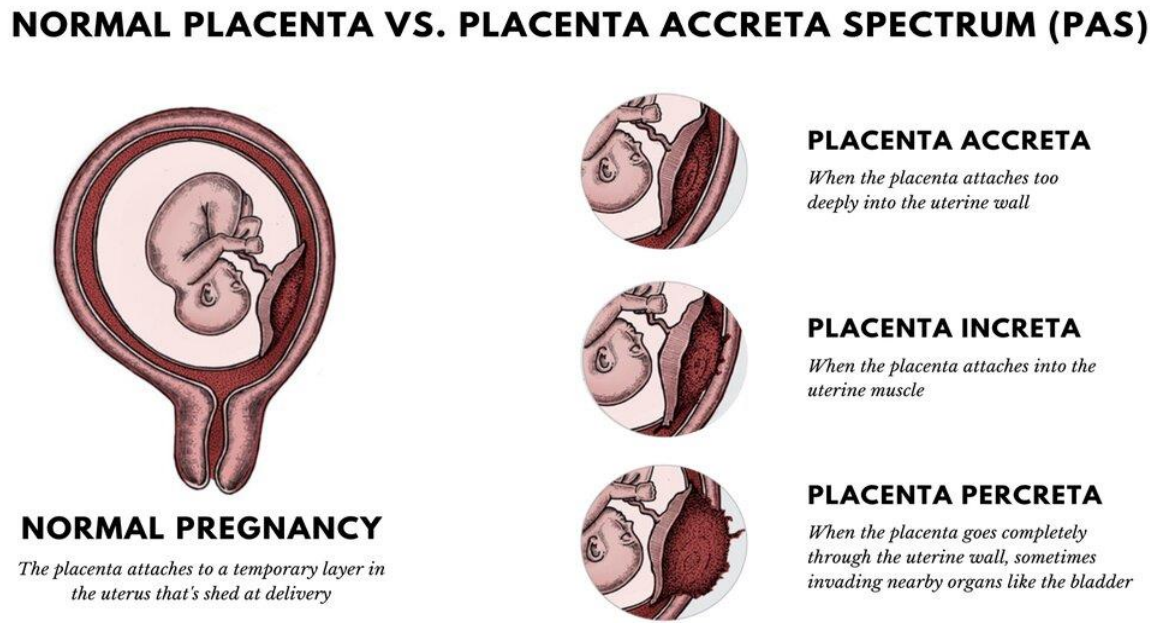
Bleeding in the third stage of labor

Reasons:

- delay of parts of the placenta or its membranes;
- pathological attachment of the placenta;
- pinching of the placenta.

The amount of blood loss depends on the type of placental attachment disorder: complete, partial adhesion of the placenta.

Classification of anomalies of placentation:



Firm (compact) attachment of the placenta:

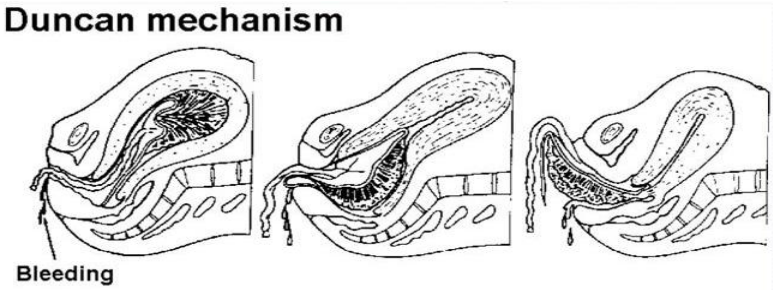
placenta accreta - pathological attachment of the placenta to the endometrium (porous layer is absent);

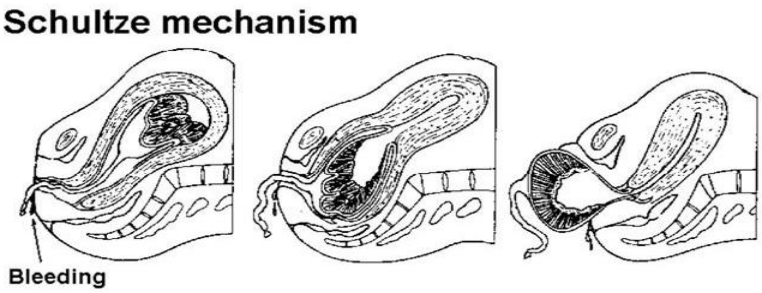
Penetration of the placenta:
placenta increta – penetration into the myometrium;
placenta percreta – invasion of the placenta the whole myometrium
The firm attachment of the placenta or its penetration can be complete (not accompanied by bleeding) and partial (accompanied by considerable bleeding due to detachment of parts of the placenta)
Reasons for pathological attachment of the placenta - changes in the structure of the porous layer of the basal decidual membrane due to:

- ➢ chronic endometritis,
- ➢ cicatricial and dystrophic changes after previous abortions or intra-uterine interventions,
- ➢ insufficient development of the uterus,
- ➢ decrease in the activity of trophoblast enzymes,
- ➢ pathological location of the placenta.

Clinical displays:
1. There are no signs of detachment of the placenta for 30 minutes without considerable blood loss - pathology of adherent or penetrated placenta.
2. Bleeding begins right after the birth of the afterbirth - delay of parts of the placenta or its membranes.
3. Bleeding begins after the birth of the child without detachment of the placenta – pinched placenta, an incomplete penetration of the placenta.
Algorithm for medical help:
1. Catheterization of a peripheral or central vein depending on the volume of blood loss and conditions of the woman.
2. Empty the bladder.
3. Check for signs of detachment of the placenta and deliver the placenta using manual maneuvers.
Signs of placental separation:

- The uterus becomes firm, round in shape and rises up.
- Lengthening of the umbilical cord.
- Sudden gush of blood

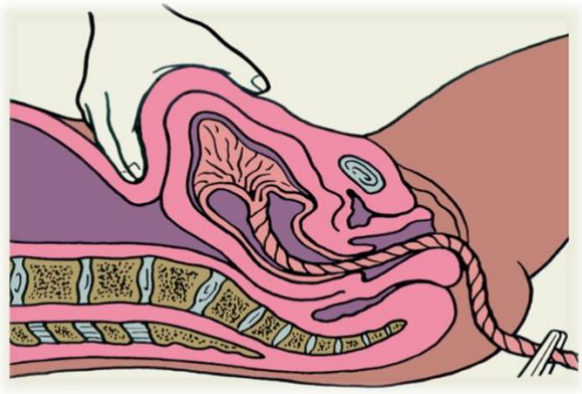


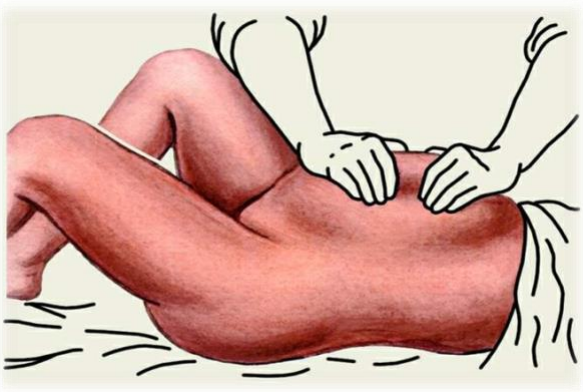


- The time from fetal delivery to delivery of the placenta
- Signs of placental separation:

a. The uterus becomes globular in shape and firmer.
b. The uterus rises in the abdomen.
c. The umbilical cord descends three (3) inches or more further out of the vagina.
d. Sudden gush of blood.

4. In case of pinching of the placenta, external massage of the uterus, external maneuvers for delivering the placenta.





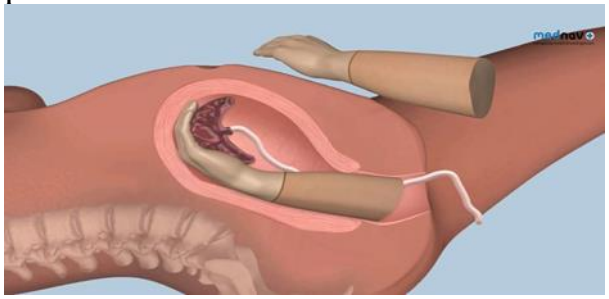
Crede-Lazarovich's maneuver Abuladze's maneuver

Abuladze's maneuver-after gentle massage of the uterus, take the anterior-abdominal wall with both hands into a longitudinal fold and ask the woman to push.
Crede-Lazarovich's maneuver- take the bottom of the uterus, the thumb is on the front wall of the uterus, the palm is on the bottom, and four fingers are on the back of the uterus.

5. In case of delay of parts of the placenta or its membranes - manual examination of the uterus cavity under intravenous narcosis.

6. If placental separation has not occurred and there is no bleeding, wait 30 minutes; manual detachment of the placenta and delivery of the placenta.

7. If bleeding occurs - urgent manual detachment of the placenta and deliver the placenta under i\v narcosis.



8. Introduction uterotonic agents – 10-20 units of oxytocin i\v in 400 ml of physiological solution by droplets.
9. If true adherence or penetration of the placenta – laparotomy, hysterectomy without the uterine appendages.
10. Evaluate the volume of blood loss and restore the blood volume (treatment of hemorrhagic shock).

Early (primary) postpartum hemorrhage

Reasons for early postpartum hemorrhage:

- hypotonic and atonic uterus (in 90% of the cases);
- delay of parts of the placenta or membranes;
- trauma to the birth canal;
- coagulation disorders (afibrinogenemia, fibrinolysis);
- Blood coagulation disorders

- **Reasons of hypotonic and atonic uterus:**

- disorder of the functional ability of the myometrium (preeclampsia, endocrinopathy, somatic diseases, tumors of the uterus, seam on the uterus, big fetus, polyhydramnios, multiple pregnancy and others);
- overexcitation with the following exhaustion of the function of the myometrium (prolonged labor), operative labor, taking drugs that reduce the tone of the myometrium (spasmolytic, tocolytics, hypoxia during delivery, etc.);
- disorder of the contractive functions of the myometrium due to disorder of biochemical processes, correlation of neurohumoral factors (estrogen, acetylcholine, oxytocin, choline esterase, progesterone, prostaglandin);
- disorders in the process of attachment, detachment and discharge of the placenta and its membranes;
- idiopathic (not established).

Hemorrhage can be of 2 kinds:

- Bleeding begins immediately after childbirth, massive (after a few minutes> 1000 ml); the uterus remains hypotonic, does not contract, hypovolemia, hemorrhagic shock develops rapidly;
- Bleeding begins after contraction of the uterus, blood flows in small portions, blood loss gradually increases. The alternation of uterine hypotonia with restoration of tone is characteristic. The bleeding stops and starts again.

Steps of management:

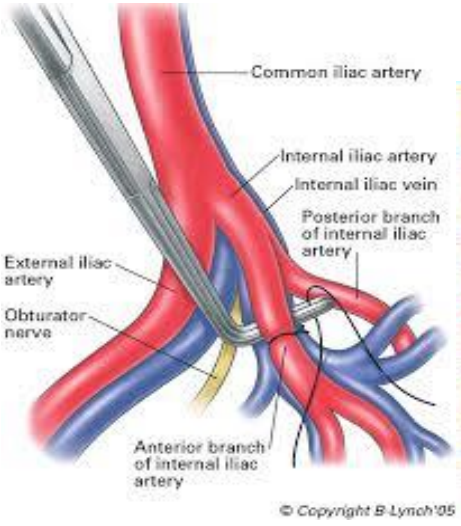
1. **General observation:**

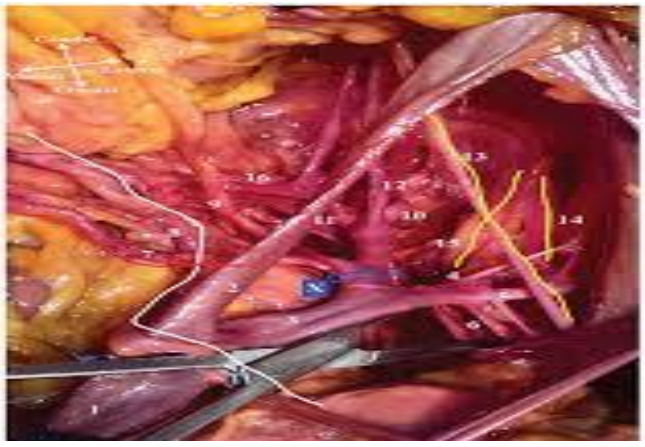
- evaluation of blood loss
- evaluation of the condition of the woman: complaints, BP, pulse rate, color of the skin and mucous membranes, amount of urine, presence and stage of hemorrhagic shock.

2. **Urgent laboratory tests:**

- determine the level of hemoglobin, hematocrit;
- coagulogram (amount of thrombocytes, prothrombin index, level of fibrinogen, coagulation time of blood);
- blood type and Rhesus factor;
- biochemical test if indicated.

3. Catheterization of peripheral or central vein depending on the size of blood loss and conditions of the woman.
4. Empty the urinary bladder.
5. Begin or continue introducing uterotonics: 10-20 units of oxytocin i/v in 400 ml of physiological solution.
6. Perform manual inspection of the uterine cavity under intravenous narcosis (evaluation of the integrity of the uterine walls, especially the left wall, remove clots of blood or the rest of the placenta or its membranes).
7. Examine the birth canal and restore its integrity.
8. External massage of the uterus.
9. In case of continuation of bleeding introduce 800 mkg of misoprostole rectally.
10. Restore blood volume and blood loss (treatment of hemorrhagic shock).
11. If bleeding continues, blood loss is 1,5% or more of the woman's body weight – treatment is operative: hysterectomy without the uterine appendages, if the bleeding continues – ligation of the internal iliac arteries.





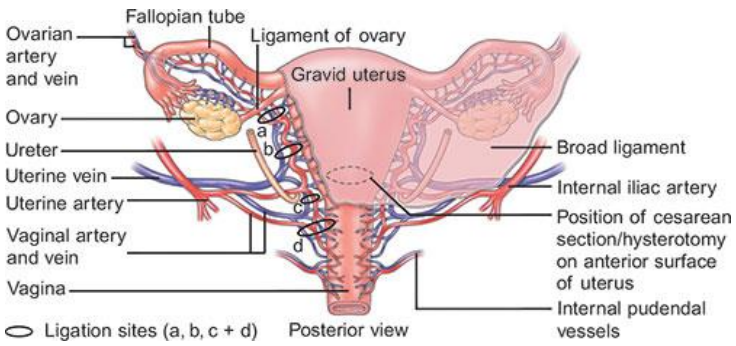
12. During preparation for operative treatment, to reduce blood loss, bimanual external or internal compression of the uterus.
13. If bleeding continues after hysterectomy - hard tamponade of the abdominal cavity and vagina (the abdominal cavity is not sutured up until the bleeding stops).

Postpartum secondary (late) hemorrhage

Main causes for late postpartum hemorrhage:

- delay of parts of the placenta or its membranes;
- discharge of necrotic tissue after delivery;
- separation of sutures on the wound on the uterus (after C-section or ruptured uterus).

Late postpartum hemorrhage occurs 7-12 days after delivery.



Steps of managment:

1. Evaluation of blood loss
2. Catheterization of peripheral or central vein.

3. Instrumental revision of the uterine cavity under i\v narcosis.
4. I\v introduction of uterotonics (oxytocin 10-20 units in physiological solution - 400,0 or 0,5 mkg of methylergometrine).
5. If the bleeding continues – misoprostol 800 mkg rectally.
6. Restore blood volume.
7. If blood loss > 1,5% of the woman's body weight – laparotomy, hysterectomy, if it still continues – ligation of the internal iliac arteries.

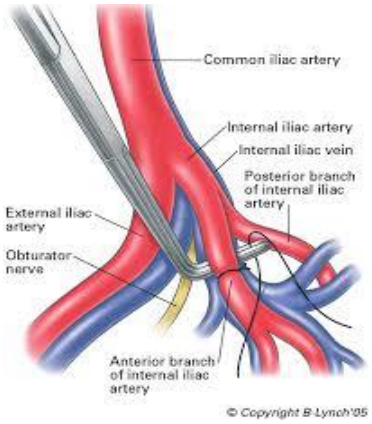
Blood coagulation disorders (postpartum afibrinogenemia, fibrinolysis):
- restore blood volume;
- correct hemostasis.

Prevention of postpartum hemorrhage:

1. During pregnancy:
- evaluate the risk factors for the occurrence of hemorrhage;

Factors which assist in the occurrence of hemorrhage in the postpartum period

Previous pregnancy	Factors, which occurred during the pregnancy	Factors, which occurred during the delivery
Primipara	Complete placental presentation	Stimulation of delivery
More than 5 deliveries in anamnesis	Placental detachment	Long or difficult delivery
Pathology in detachment or discharge of the placenta	Hydramnion	Fast delivery
Operations on the uterus in the anamnesis, including C-sections	Multiple pregnancy	Emergency Cesarean section
Long or difficult delivery in anamnesis	Intrauterine fetal death	Delivery with obstetrical forceps
Background diseases –cardio-vascular diseases, diabetes, coagulation disorders	Severe pre-eclampsia, eclampsia	Chorioamnionitis



Anemia	Hepatitis	DIC – syndrome
Hysteromyoma	Conditions connected with anemia	General or epidural anesthesia

- Diagnostics and treatment of anemia;
- Hospitalization, readiness to give medical help to pregnant women of high risk for hemorrhage: antenatal hemorrhage, hemorrhage in labor, polyhydramnios, multiple pregnancy, big fetus.

2. During delivery:

- anesthesia during labor;
- avoid prolong labor;
- **Active management of third stage of labor**. The underlying principle in active management is to excite powerful uterine contractions within one minute of delivery of the baby (WHO) by giving parenteral oxytocic. This facilitates not only early separation of the placenta but also produces effective uterine contractions following its separation. The advantages are — (a) to minimize blood loss in third stage approximately to 1/5th and (b) to shorten the duration of third stage to half.

Injection oxytocin 10 units IM (preferred) or methergin 0.2 mg IM is given within 1 minute of delivery of the baby (WHO). The placenta is expected to be delivered soon following delivery of the baby. If the placenta is not delivered thereafter, it should be delivered forthwith by **controlled cord traction (BrandtAndrews**) technique after clamping the cord while the uterus still remains contracted. If the first attempt fails, another attempt is made after 2–3 minutes failing which another attempt is made at 10 minutes. If this still fails, manual removal is to be done. Oxytocic may be given with crowning of the head, with delivery of the anterior shoulder of the baby or after the delivery of the placenta. If the administration is mistimed as might happen in a busy labor room, one should not be panicky but conduct the third stage with conventional watchful expectancy.

Controlled cord traction (modified Brandt-Andrews method)—The palmar surface of the fingers of the left hand is placed (above the symphysis pubis) approximately at the junction of upper and lower uterine segment (Fig. 12.27). The body of the uterus is pushed upwards and backwards, toward the umbilicus while by the right hand steady tension (but not too strong traction) is given in downward and backward direction holding the clamp until the placenta comes outside the introitus.

Fundal pressure—The fundus is pushed downwards and backwards after placing four fingers behind the fundus and the thumb in front using the uterus as a sort of piston. The pressure must be given only when the uterus becomes hard. If it is not, then make it hard by gentle rubbing. The pressure is to be withdrawn as soon as the placenta passes through the introitus.

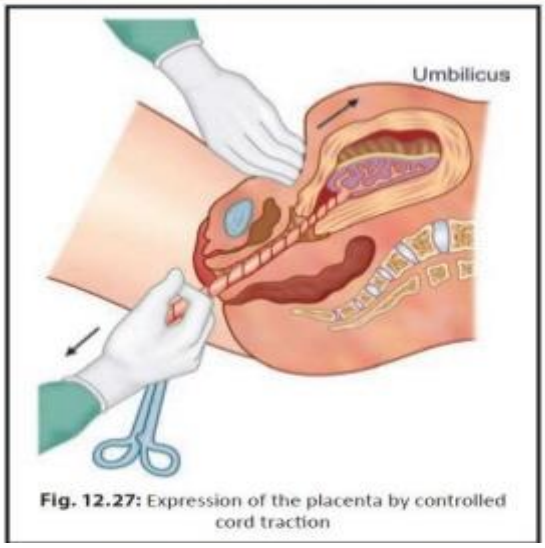


Fig. 12.27: Expression of the placenta by controlled cord traction

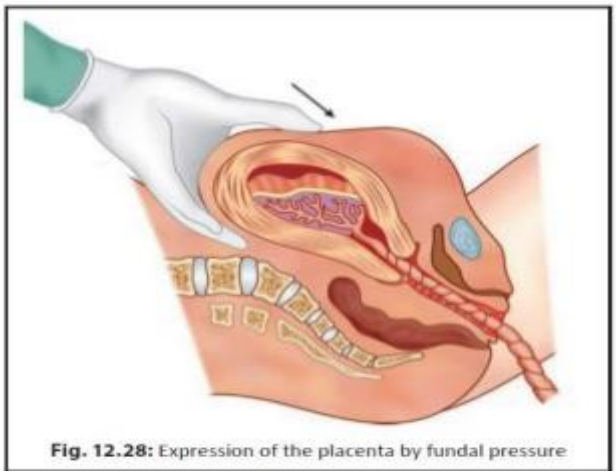


Fig. 12.28: Expression of the placenta by fundal pressure

- use uterotonic during the third period of labor;
- routine observation and evaluation of the integrity of the placenta and its membranes;
- prevention of trauma during labor.

3. After labor:

- Inspection and examination of the birth canal;
- Attentive supervision throughout 2 hours after delivery;
- In woman of high risk – i/v introduction of 20 units of oxytocin for 2 hours after the delivery.

Methods for determining the volume of blood loss

1. **Libov's Method**

Volume of blood loss is determined by weighing the napkins used, which are soaked in blood

Volume of blood loss = B / 2 x 15 % (blood loss less than 1000 ml) or x 30% (blood loss more than 1000 ml).

Where B - weight of the napkins, 15 % and 30 % - error size (amniotic fluid, physiological solution).

2. Nelson's formula

The percentage ratio of the total amount of blood loss is figured:

$$\frac{0{,}036 \times \text{original blood volume}}{\text{body weight}} \times \text{hematocrit}$$

$$\text{original blood volume (ml/kg)} = \frac{24}{0{,}86 \times \text{original hematocrit}} \times 100$$

3. hematocrit

	ume of blood loss, ml
	o 500

1053-1050	38-32	1000
1049-1044	30-22	1500
Less than 1044	Less than 22	More than 1500

4. Algover's Shock index

$$\text{Shock index} = \frac{\text{Heart rate}}{\text{BPs}}$$

W

Normally Algover's index = 1.

By determining the index size it is possible to conclude about the size of blood loss

Algovera's index	Volume of blood loss (% of blood volume)
0,8 and less	10 %
0, 9-1, 2	20 %
1, 3-1,4	30 %
1,5 and more	40 %

NB! Algover's index is not informative in patients with hypertension

5. Moore's hematocrit method

$$BL = BV\ (n) \times (Ht\ (n) - Ht\ (a)) / Ht\ (n)$$

Where:

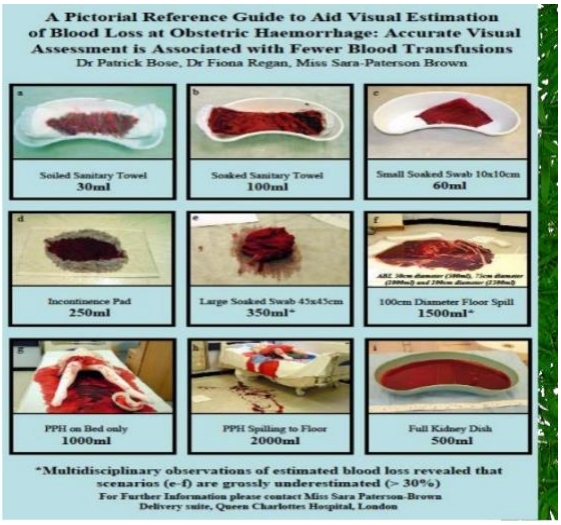
BL – blood loss; BV (n) – normal blood volume; Ht (n) – normal hematocrit (in woman – 42);

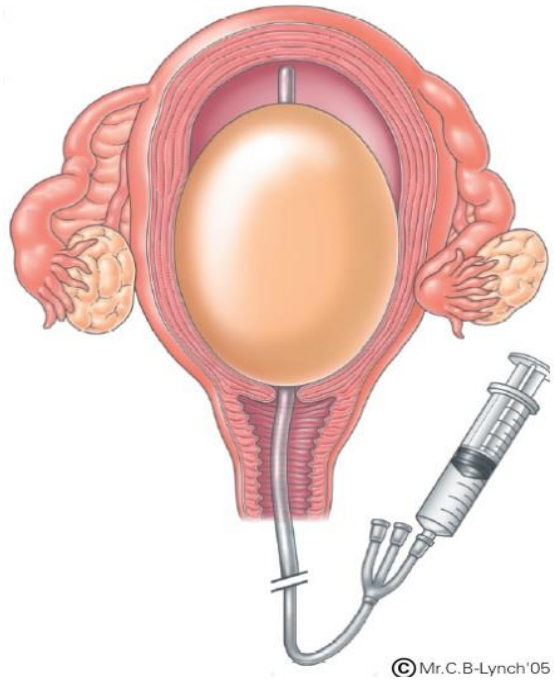
Ht (a) – actual hematocrit determined after blood loss is stopped and hemodynamics are stabilized

For rough amount of blood loss in pregnant women it is possible to use the modified Moore's formula:

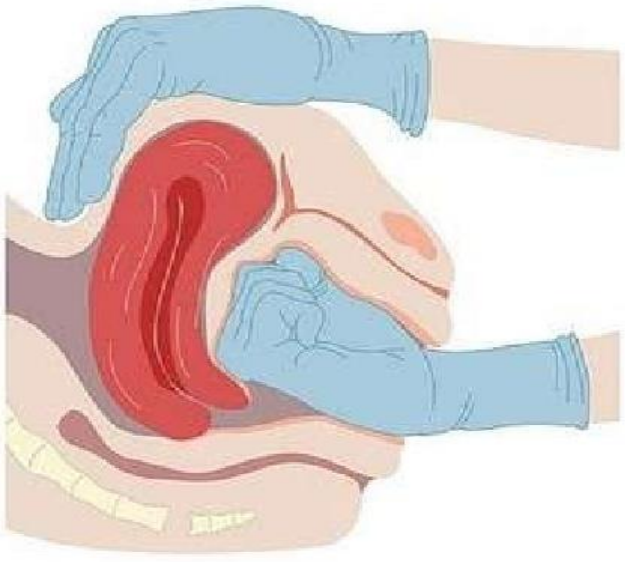
$$BL = M \bullet 75 \bullet \frac{0{,}42 - Ht\ (a)}{0{,}42}$$

Where: BL – blood loss; (ml); M – woman's body weight (kg); Ht (a)- patient's actual hematocrit (l/l)

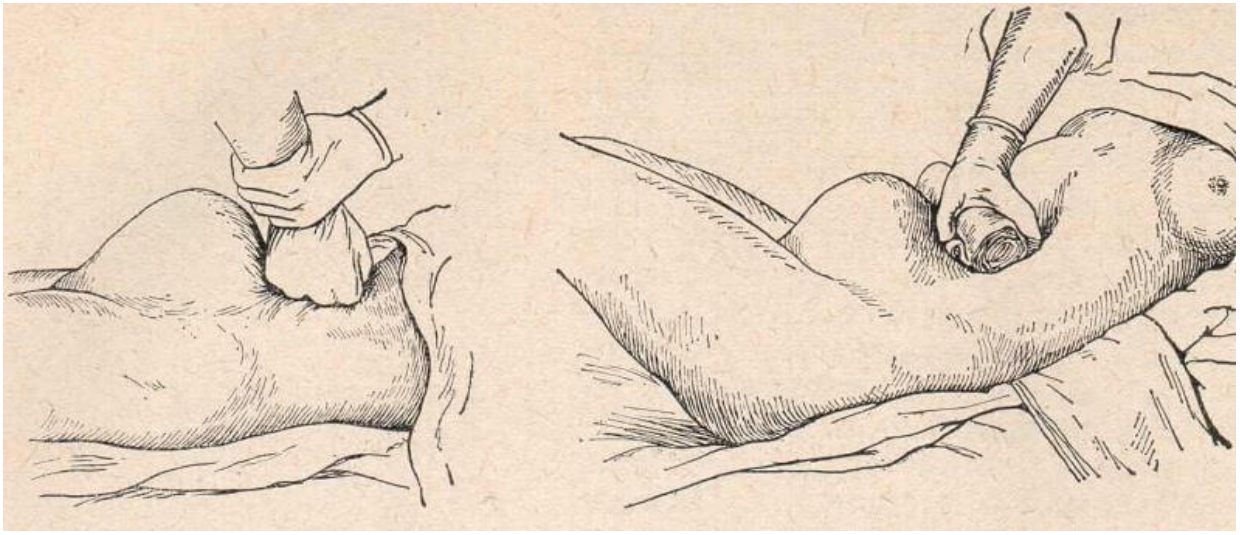




Baloon tamponade of uterus



Bimanual compression of the uterus



Compression of the aorta

Coagulopatic bleedings

Any congenital or acquired coagulopathies can lead to profuse postnatal bleeding (delay of dead fetus in the uterus, amniotic fluid embolism, premature detachment of a normally located placenta, rupture of the uterus, sepsis, massive transfusions, severe pre-eclampsia and eclampsia, extra-genital pathology). Therapy can result in disorder in the system of hemostasis during delivery with use of anticoagulants, long hemodilution. It should be remembered, that profuse bleeding can lead to coagulopathy.

Bleeding due to intrauterine death of the fetus

If childbirth does not occur right after death of the fetus, severe coagulopathy can develop, caused by the discharge of thromboplastin from the tissue of the fetus. Treatment is immediate delivery and correction of the coagulation disorder. Induction of labor is conducted by intravenous introduction of oxytocin or prostaglandin. It is necessary to avoid hyperstimulation of labor, especially after 28 weeks, in connection with risk of rupture of the uterus in such patients.

Managing Maternal Haemorrhage

Vital Signs

Airway

– Provide adequate ventilation

– Assess need for intubation

Breathing

– Supplemental O2 5-7 L/min by tight face mask

Circulation

– Pallor, delayed capillary refill, and decreased urine output can indicate compromised blood volume without change in BP or HR

– Decreased urine output, decreased BP, and tachycardia may be late signs of compromise

Actions

• Notify team

• Bring cart & medications to patient room

• Activate Massive Transfusion Protocol

Infusions

• Start 2nd large bore IV (16 gauge if possible)
• Ringers Lactate (RL) replaces blood loss at 2:1
• Prepare for transfusion
• Blood coagulation factors
• Warm blood products and infusions to prevent hypothermia, coagulopathy, and arrhythmias

Medication for Uterine Atony

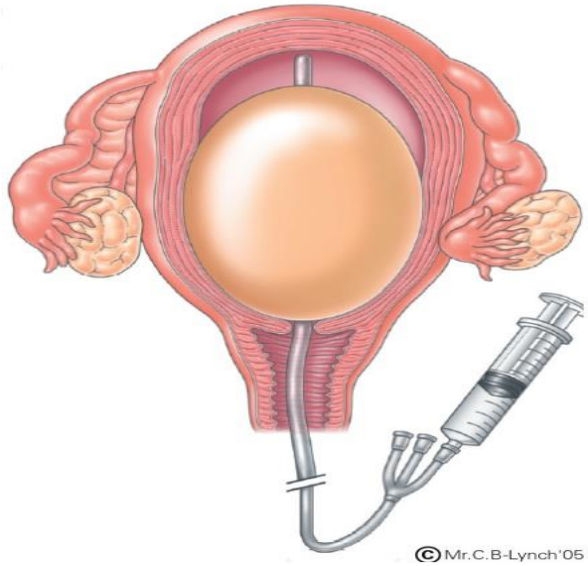
oxytocin (Pitocin) 10-40 units per 500-1000mL solution
methylergonovine (Methergine) 0.2 milligrams IM
Avoid with hypertension prostaglandin f2 alpha (Hemabate) 250 micrograms IM (may repeat in q15 minutes, maximum 8 doses)
Avoid with asthma; use with caution with hypertension misoprostol (Cytotec) 800-1000 micrograms PR, 600 micrograms PO, or 800 micrograms SL

<table>
<tr><th colspan="5">First stage (blood loss <1000 ml)</th></tr>
<tr><td rowspan="4">Etiology</td><td>Tone</td><td colspan="2">Manual inspection of the uterine walls</td><td rowspan="6">simultaneously</td></tr>
<tr><td>Tissue</td><td>One-time</td><td></td></tr>
<tr><td>Trauma</td><td>Suturing, laparotomy</td><td></td></tr>
<tr><td>Thrombin</td><td colspan="2">Transfusion of coagulation factors</td></tr>
<tr><td>Priority</td><td>Carbetocin, oxytocin</td><td>Methylergometrine</td><td>prostaglandins</td></tr>
<tr><td>Primary dose</td><td>-Carbetocin-100 mcg i/v once
-Oxytocin 10 units i/m</td><td>Methylergometrine 0.2 mg i/m or i/v</td><td>Misoprostol 800 mcg per rectum</td></tr>
<tr><td>Repeated dose absence of bleeding</td><td>-Oxytocin 10 units i/v in 500 ml solution 60 min.</td><td>Methylergometrine 0.2 mg i/m or i/v every 4 hors</td><td>----------</td></tr>
<tr><td>Max dose</td><td>Not more 3 l liq in day, oxytocine</td><td>3 doses(1.0 mg)</td><td>Misoprostol 800 mcg per rectum</td></tr>
</table>

Contraindication	---------	-preeclampsia -hypertension -heart diseases	-preeclampsia -asthma -glaucoma	
	10 min	**10 min**	**10 min**	
Second stage-between conservative and haemostasis				
Balloon tamponade, two handed uterine compression, abdominal aorta compression				

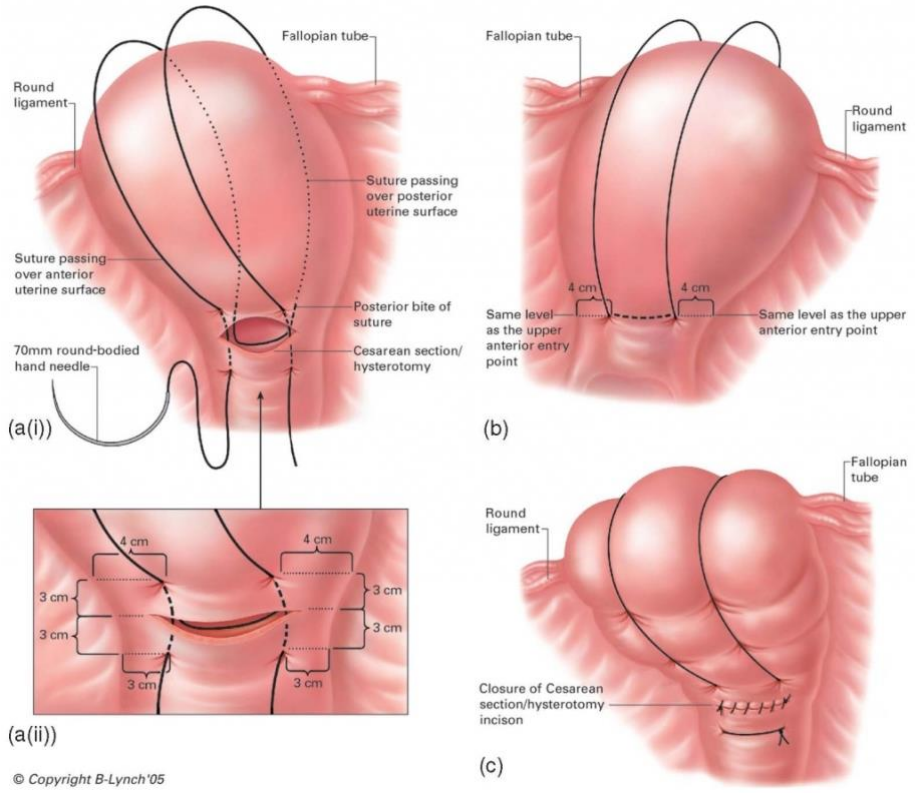
Third stage- surgical - laparotomy		
≥1500 ml	>1500 ml	Angiographic embolization
Injection of prostaglandins in the myometrium, local uterine hypothesis		
Ligatures on ovarian uterine vessels **Compression suture on the uterus**	Ligation of a lacerated iliac artery, ovarian vessels	
Tight tamponade of the pelvis and vagina	Total subtotal hysterectomy	

Intrauterine balloon tamponade



Surgical Interventions

May be a life-saving measure and should not be delayed pending correction of coagulopathy, the most common reason for the delay



B-lynch suture

Infusion transfusion therapy of obstetric hemorrhage									
Blood loss			**Total Transfusion of circ-blood**	**Infusion and transfusion environment**					
Volume of Circ-blood	**% of W.body**	**Blood loss (ml)**		**Crystolloids**	**colloids**			**weight**	**Thrombo concetrat**
					Synthetic (Gelofusine)	**Natural**			
						plasma	**Albumin 10%**		
10-20%	1-1.5%	500-1000	200-300 (2.5L)	10-15 ml/kg	10 ml/kg	------	-------	-------	----------
20-30%	1.5-2%	1000-1500	200 (3L)	10 ml/kg	10 ml/kg	5-10 ml/kg	-------	5 ml/kg	----------
30-40%	2-2.5%	1500-2000	180(4L)	7 ml/kg	7 ml/kg	10-15 ml/kg	200 ml	10-20 ml/kg	cryopre
40-70%	2.5-3.6%	2500-3000	170 (5L)	7 ml/kg	10-15 ml/kg	15-20 ml/kg	200 ml	30 ml/kg	Cryopre

>70%	>3.6%	>3000	150 (>6L)	10 ml/kg	20 ml/kg	>20 ml/kg	>200 ml	>30 ml/kg	4-10 uni

MATERIALS FOR ACTIVATION OF STUDENTS DURING THE LECTURE: QUESTIONS, SITUATIONAL TASKS, ETC.

QUESTIONS:

- What pathological conditions may cause obstetrical bleeding?
- What is the classification of placenta previa, premature detachment of a normally located placenta and postpartum haemorrhage?
- What are modern views on etiology and pathogenesis of placenta previa?
- What are the methods of examination in placenta previa and premature detachment of a normally located placenta?
- What are the principles and methods of treatment of placenta previa and premature detachment of a normally located placenta?
- What is the differential diagnosis of placenta previa and premature detachment of a normally located placenta?
- Obstetrical tactics and treatment of placenta previa and premature detachment of a normally located placenta?
- Prevention and prophylactics of placenta previa and premature detachment of a normally located placenta?
- The classification and reasons of postpartum haemorrhage?
- What are the risk factors for postpartum haemorrhage occurrence?
- Modern methods of blood loss evaluation?
- Emergency help at postpartum haemorrhage?

TEST TASKS

Direction: For each of the multiple-choice questions select the lettered answer that is the one best response in each case.

1. 1. At survey of a placenta which was just born, presence of defect in size of 2x3 cm was fixed. Bleeding is not present. What tactics is most significant?

A. External massage of a uterus.
B. Assignment of uterotonic agents
C. Manual inspection of uterine cavity.
D. Observation over the puerperal women
E. Instrumental inspection of uterine cavity

2. At twice pregnant women 25 years old in the third stage of labor the bleeding started with placental defect found. At manual uterine inspection small part of the placenta fixed to the myometrium was determined. Tactics of the doctor?

A. Laparotomy, a hysterectomy.
B. Instrumental extraction of the placental remnant
C. Application of uterotonic agents
D. Blood transfusion.

E. Prophylaxis of a puerperal uterine inflammation

3. At the puerperal women a massive bleeding after natural twins birth occured. The placenta and birth canal tissues remained intact. The uterine fundus is higher than a an umbilicus, the uterus at a palpation soft, does not react to uterotonics introduction. What is most common reason of bleeding?

A. Damage of uterine cervix
B. Atony of a uterus
C. Uterine rupture
D. A delay of parts of a placenta
E. A hypotonia of a uterus

4. At the parturient woman with the serious form of a preeclampsia right after the newborn birth bleeding began. The placenta is whole, birth canal tissues intact. The uterine fundus is lower than umbilicus 2 cm, dense. At external uterine massagethe bleeding increased, a blood is liquid and without clots. What diagnosis can be assumed?

A. Uterine rupture
B. A hypotonic bleeding
C. Placental parts delay in uterus
D. A coagulopatic bleeding, the DIC syndrome
E. An embolism by amniotic fluid

5. During caesarian section operation due to.complete placental presentation, after placenta removal severe bleeding from placental platform site started. The remnants of placental tissue can not be removed manually, uterus is soft, badly contracted. The diagnosis of a true partial increment of placenta is put. Specify the most rational tactics to stop bleeding.

A. To enter intravenously uterotonics.
B. To remove instrumentally the remnants of a placental tissue.
C. To carry out sewing of bleeding sites.
D. To carry out the main vessels ligation.
E. To carry out a hysterectomy without appendages.

6. Primapara, 22 y.o., after delivery of a newborn, 4000 gr, the haemorrhage has started. Bloodloss – 20 % of CBV (Circulating blood volume), BP 100/60 mm, shock index – 1. Your diagnosis:

A. Hemorrhagic shock I degree
B. Hemorrhagic shock III degree
C. Thromboembolic shock
D. Hemorrhagic shock II degree
E. Septic shock

7. In Woman-in-labor in the early puerperal period haemorrhage appeared. Bloodloss is 1500 ml (1,8 %). General state is severe, the consciousness is confused, anergic stupor, anxiety, body t˚ - 35,7˚C, pale skin, acrocyanosis. Tachicardia 130-140 b/min, CVP (Central venous pressure) – 20 mm, RR (respiration rate) 40 in min, diuresis per hour 15-20 ml/h, Ht –0,25, shock index – 1,4, Hb –70 g/l. What should be the doctor's tactics?

A. Cold on the lower abdomen.

B. Laparotomy. Total hysterectomy without appendages.
C. Manual revision of uterine cavity and massage of the uterus.
D. Applying of ligating clamps on parametrium.
E. Introduction of Ether tampon.

8. At multipara with placental presentation the uterine haemorrhage have appeared. total blood loss – 500 ml, BP 100/60 mm, Ps – 100 in 1 min, pale skin. Determine the shock index:

A. 1.5
B. 0.5
C. 1.0
D. 0.8
E. 2.0

9. At woman in early puerperal period haemorrhage started. Total blood loss –1000 ml, BP –90/70 mm, Ps – 120 b/min, pale skin, cold sweat, oliguria. Determine the grade of hemorrhagic shock:

A. 0
B. I
C. II
D. III
E. IV

10. At woman in early puerperal period haemorrhage started. Total blood loss –1000 ml, BP –90/70 mm, Ps – 120 b/min, pale skin, cold sweat, oliguria. Determine the total volume of infuse therapy in litres in connection with total blood loss:

A. 2
B. 1.5
C. 2.5
D. 1
E. 3

Answer key

1	C	6	D
2	A	7	B
3	B	8	C
4	D	9	C
5	E	10	B

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