MINISTRY OF HEALTH OF UKRAINE
ODESA NATIONAL MEDICAL UNIVERSITY

International Faculty

Department of obstetrics and gynecology

CONFIRMED by
Vice-rector for scientific and pedagogical work
Eduard BURIACHKIVSKYI
«29» August, 2024

METHODOLOGICAL RECOMMENDATIONS FOR LECTURE

International Faculty, Course V

Discipline “Obstetrics and Gynecology”

Lecture №3. Topic: Miscarriage. Preterm labor.

Approved:

Meeting of the Department of Obstetrics and Gynecology of Odesa National Medical University

Protocol No. 1 dated August 29, 2024.

Head of the Department_____ (Ihor GLADCHUK)

Developer:
Ph.D., assistant professor of
obstetrics and gynecology department_____(N. Nastradina)

LECTURE №3: **MISCARRIAGE. PRETERM LABOR.**

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.

PLAN AND ORGANIZATIONAL STRUCTURE OF THE LECTURE.

№	The basic stages of the lecture and their contents	Type of lecture, equipment	Division of time
1	**Preparatory stage:** Defining the educational purposes.		2 min.
2	Providing positive motivation		3 min.

3	**Basic stage:** Teaching the lecture material. Plan: Epidemiology and incidence Neonatal outcomes after preterm birth. Endocrinology and biochemistry of labour. Causes of preterm labour Prevention and prediction of preterm labour. Management and perinatal outcomes	 Clinical Table Table Codogram Codogram	100 min 85-90% 100 min. 25 min. 15 min. 10 min. 20 min. 20 min. 20 min.
4	**Final stage:** Resume of the lecture, general summary		 5 min.
	Answer any possible questions		5 min
	Problems for student self-preparation		5 min

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.

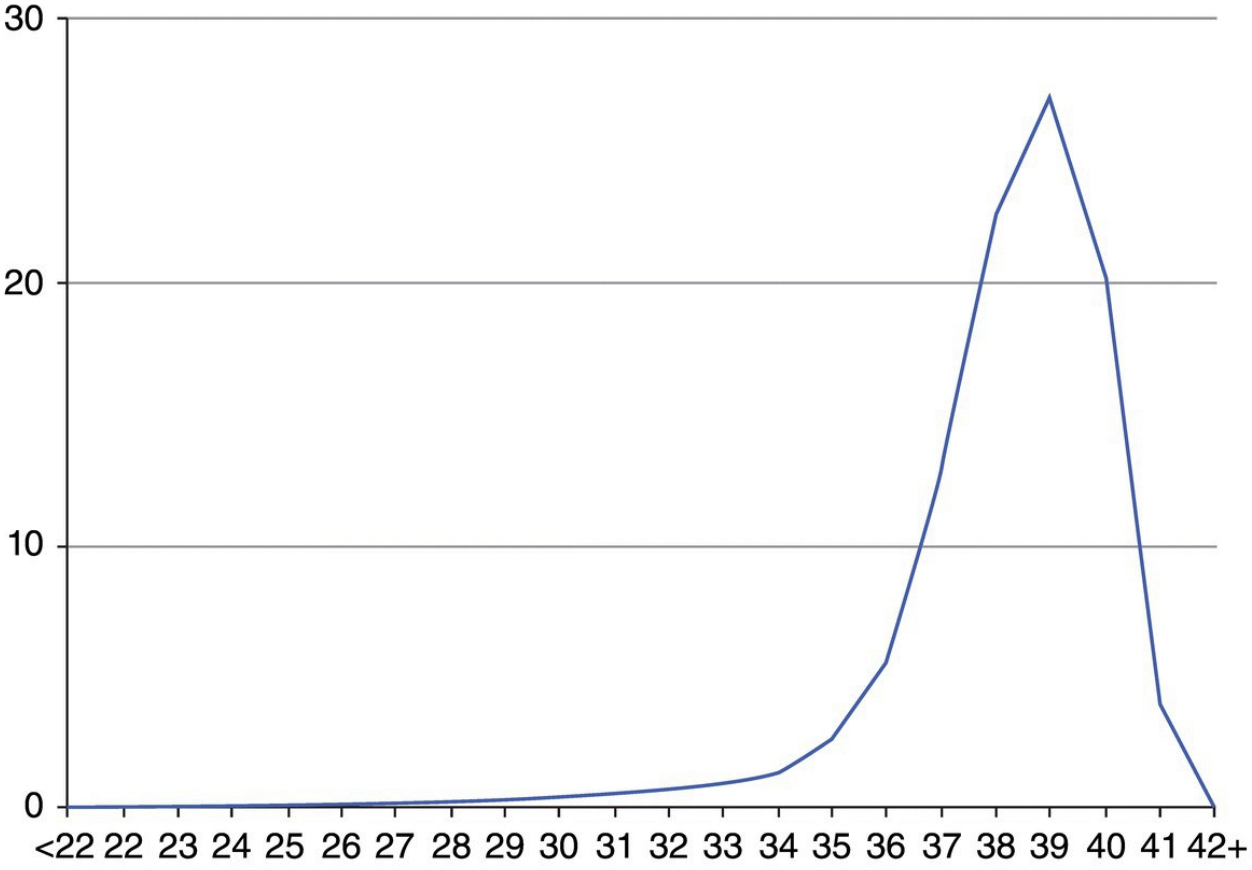


Fig. 28.2 Live birth percentages by gestation, 2011 birth cohort, England and Wales. *Source:* UK Office for National Statistics.

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

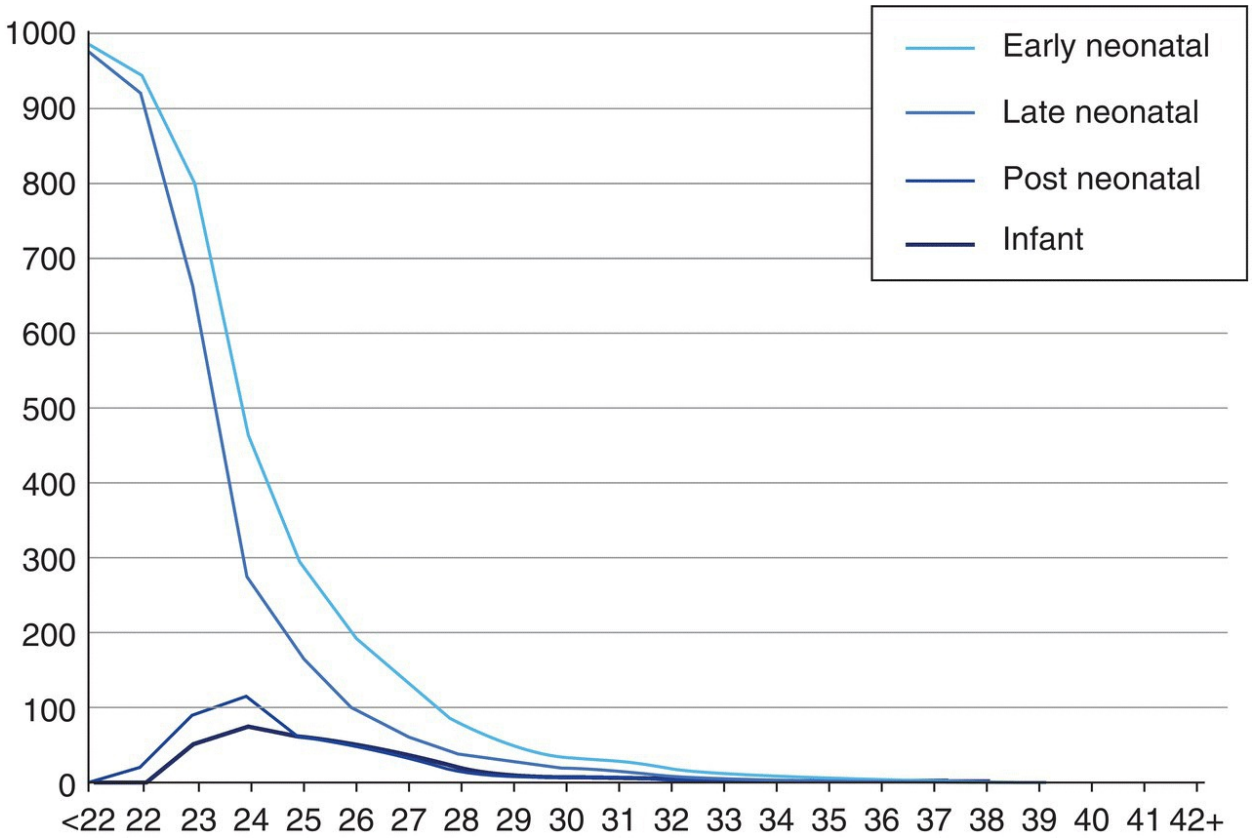
successive term birth. Marital status, cigarette smoking, environmental stress, poor nutrition and use of alcohol, coffee and street drugs (especially cocaine) have all been linked to an increased risk of preterm birth. However, many of these factors are interlinked and all are factors associated with 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.

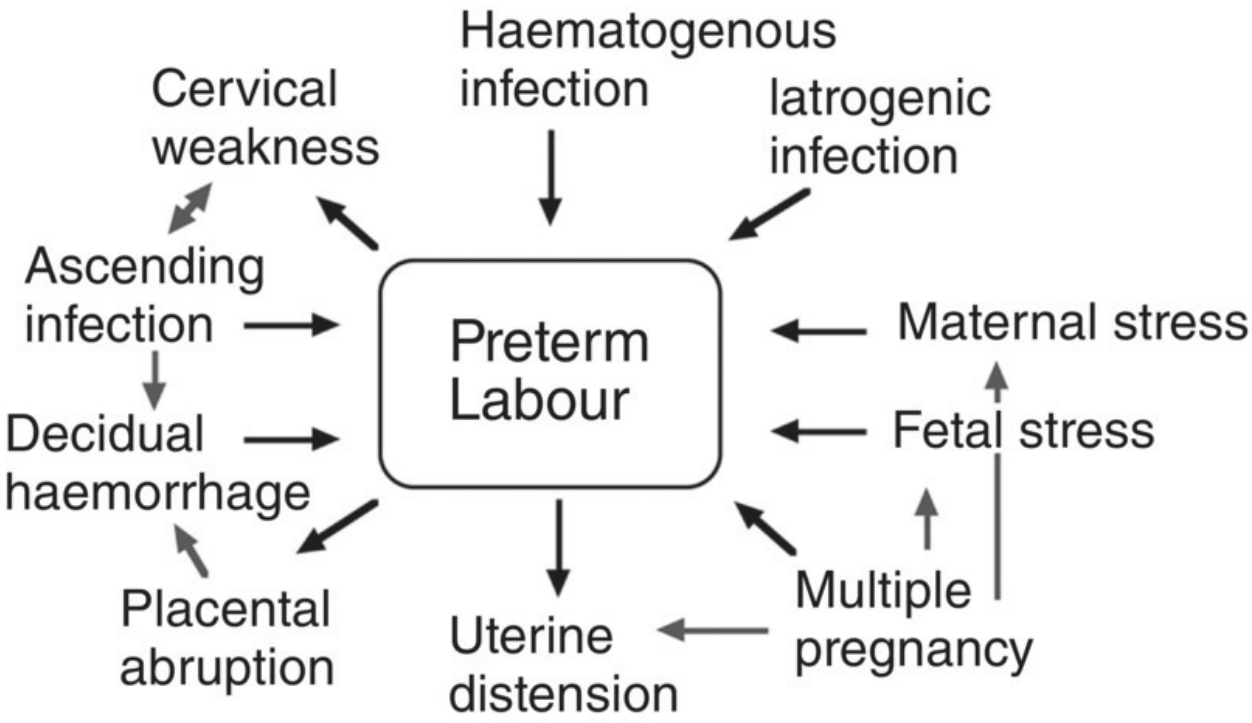


In the past, surfactant deficiency leading to neonatal respiratory distress syndrome (RDS) was the major cause of morbidity and mortality in preterm infants. Alveolar surfactant production begins at 30–32 weeks' gestation. Therefore, preterm infants born prior to 30 weeks are at highest risk. The impact 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

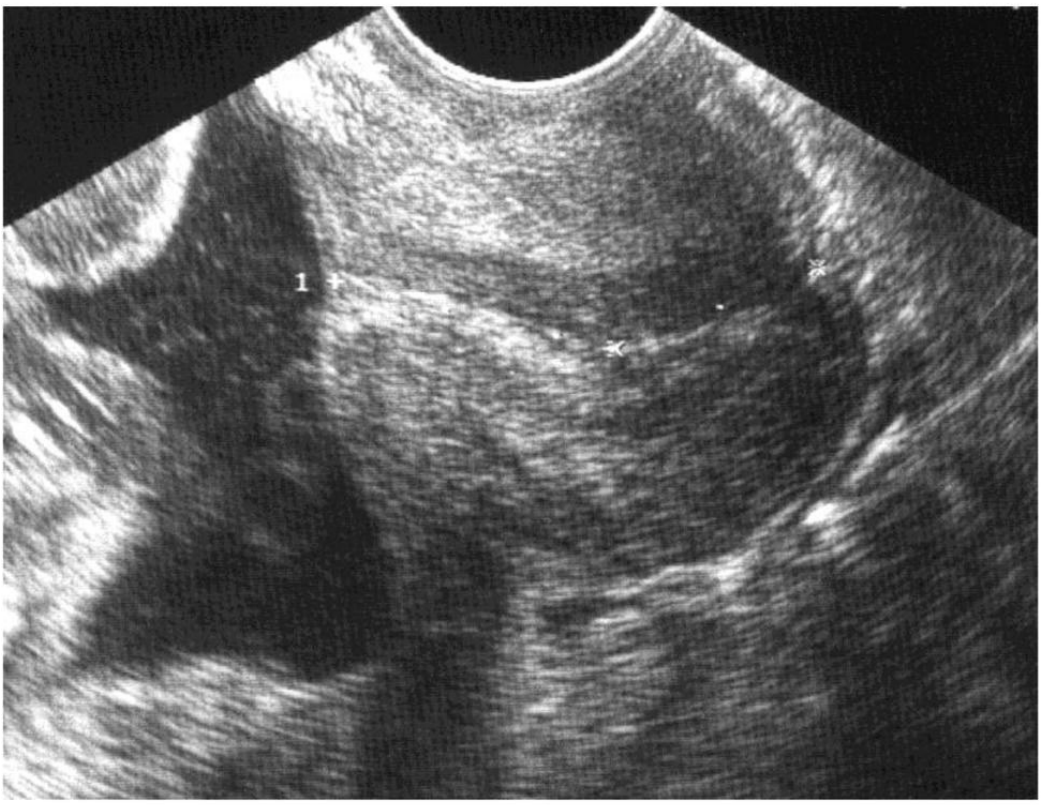
In the majority of cases of preterm labor obstetric management consists principally of attempting to suppress contractions in women who are already in established labor. As discussed in more detail later, this strategy is essentially ineffective. Obstetric strategies to reduce perinatal morbidity and 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.

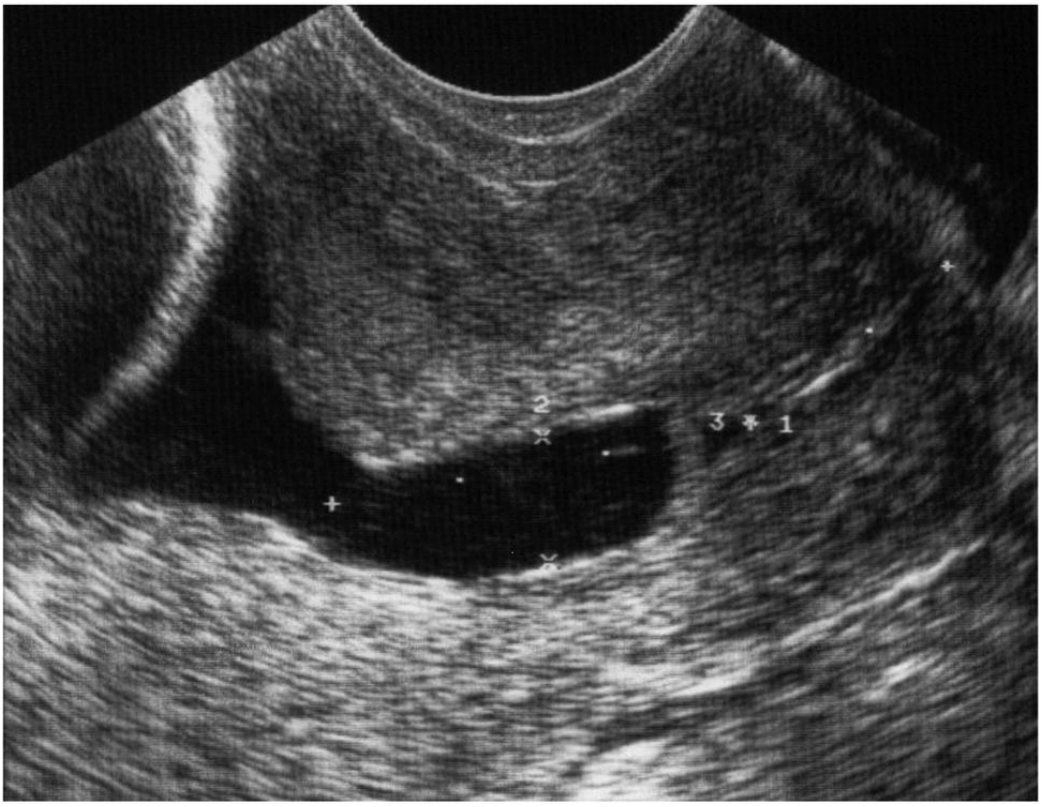
Ultrasound measurement of cervical length

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)

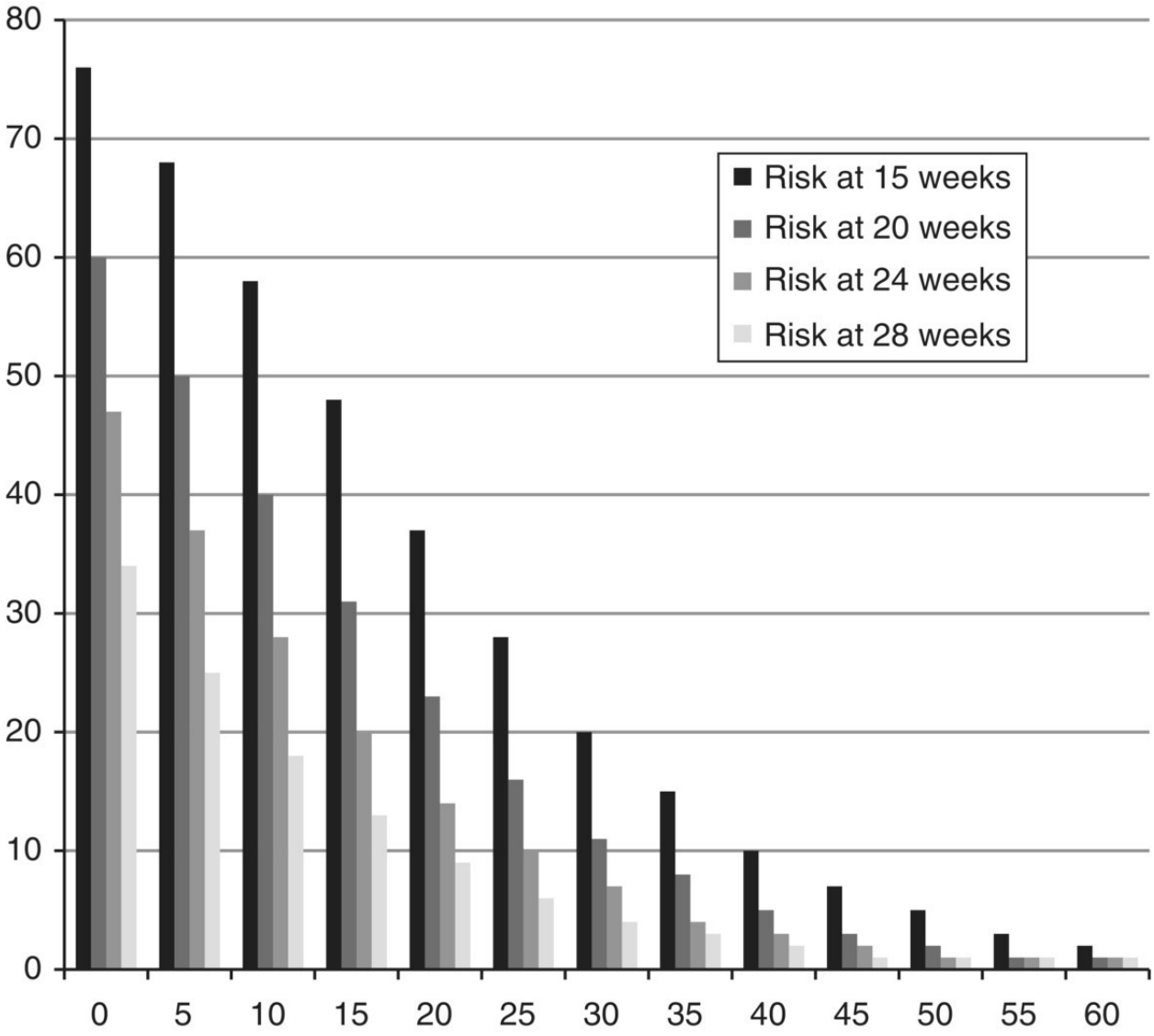


(b)



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.



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.

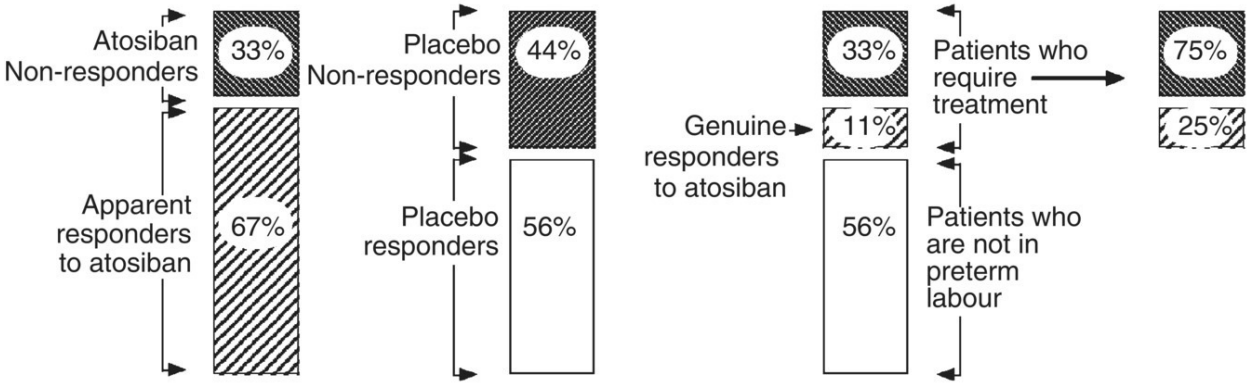


Fig. 28.7 Analysis of the 48−hour outcome data from the placebo−controlled trial of atosiban. Of all patients allocated to atosiban treatment, only 11% showed a genuine clinical response (rather than a placebo response) which represents one−quarter of those with the potential to benefit. This effect 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

EQUIPMENT AND EDUCATIONAL AND METHODOLOGICAL SUPPORT OF THE LECTURE:

- Obstetric models and obstetric instruments (pelvimeter, obstetric stethoscope, centimeter tape).
- Professional algorithms, structural-logical schemes, tables, videos.
- Results of laboratory and instrumental researches, situational tasks, patients, medical histories.
- Multimedia equipment (computer, projector, screen), TV.

RECOMMENDED LITERATURE

Basic:

1. Gladchuk I.Z. Obstetrics: student`s book / Gladchuk I.Z., Ancheva I.A. . – Vinnitsia: Nova Knyha, 2021. – 288 p.
2. Obstetrics and Gynecology: in 2 volumes. Volume 1. Obstetrics: textbook / V.I. Gryshchenko, M.O. Shcherbina, B.M. Ventskivskyi et al. (2nd edition). – «Medicina», 2018. – 392 p.
3. Hiralal Konar DC Dutta's Textbook of Obstetrics (9th Ed.) / Hiralal Konar (Ed.). – Jp Medical Ltd, 2018. – 700 p.

4. F. Gary Cunningham Williams Obstetrics (26th Edition) / F. Gary Cunningham, Kenneth Leveno, Jodi Dashe, Barbara Hoffman, Catherine Spong, Brian Casey. – McGraw Hill / Medical, 2022. – 1328 p.
5. Jeremy Oats, Suzanne Abraham Llewellyn-Jones Fundamentals of Obstetrics and Gynaecology (10th Ed) / Jeremy Oats, Suzanne Abraham. – Elsevier, 2016. – 384 p.

Additional:

1. The PROMPT-CIPP Editorial Team. (2019). PROMPT-CIPP Course Participant's Handbook: Care of the Critically Ill Pregnant or Postpartum Woman (Critical Car Prompt Practical Obstetric Multi-professional Training). – Cambridge University Press; 1st edition, 2019. – 136 p.
2. L. A. Magee The FIGO Textbook of Pregnancy Hypertension. An evidence-based guide to monitoring, prevention and management. / L. A. Magee, P. Dadelszen, W. Stones, M. Mathai (Eds). – The Global Library of Women's Medicine, 2016. – 456 p.
3. Edwin Chandraharan Handbook of CTG Interpretation: From Patterns to Physiology / Edwin Chandraharan. – Cambridge University Press; 1st edition, 2017. – 256 p.
4. Louise C. Kenny, Jenny E. Myers Obstetrics by Ten Teachers (20th ed) / Louise C. Kenny, Jenny E. Myers. – CRC Press, 2017. – 342 p.
5. J. Studd Current Progress in Obstetrics and Gynaecology. Vol 4. / J. Studd, Seang Lin Tan, F. Chervenak. – TreeLife Media (A Div of Kothari Medical), 2017. – 419 p.
6. J. Studd Current Progress in Obstetrics and Gynaecology. Vol 5. / J. Studd, Seang Lin Tan, F. Chervenak. – TreeLife Media (A Div of Kothari Medical), 2019. – 403 p.
7. J. Studd Current Progress in Obstetrics and Gynaecology. Vol 6. / J. Studd, Seang Lin Tan, F. Chervenak. – TreeLife Media (A Div of Kothari Medical), 2022. – 309 p.
8. Mark Landon Obstetrics: Normal and Problem Pregnancies, 8th Edition / Mark Landon, Henry Galan, Eric Jauniaux, Deborah Driscoll, Vincenzo Berghella, William Grobman, et al. – Elsevier, 2021. – 1280 pp.
9. Mark B. Landon Gabbe's Obstetrics Essentials: Normal & Problem Pregnancies, 1st Edition / Mark B. Landon, Deborah A. Driscoll, Eric R. M. Jauniaux, Henry L. Galan, William A. Grobman, Vincenzo Berghella. – Elsevier, 2019. – 496 pp.
10. Ian M. Symonds, Sabaratnam Arulkumaran Essential Obstetrics and Gynaecology, 6th Edition / Ian M. Symonds, Sabaratnam Arulkumaran. – Elsevier, 2020. – 480 pp.
11. Myra J. Wick Mayo Clinic Guide to a Healthy Pregnancy, 2nd Edition / Myra J. Wick. – Mayo Clinic Press, 2018. – 520 p.

INTERNET SOURCES:

- https://www.cochrane.org/
- https://www.ebcog.org/
- https://www.acog.org/
- https://www.uptodate.com
- https://online.lexi.com/
- https://www.ncbi.nlm.nih.gov/
- https://pubmed.ncbi.nlm.nih.gov/
- https://www.thelancet.com/
- https://www.rcog.org.uk/
- https://www.npwh.org/