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Preface

In the developed countries, premature infants have medico-social impacts that account for 90% of perinatal deaths and 50–60% of neurological handicap, leading to huge social burden. Thus, preterm labor and delivery is one of the most impending and significant clinical issues to be solved. Recent studies also show that the impact of prematurity is not only for the index premature infant to be born, its mother and the family, but also for their offspring.

With compiling clinical and basic evidence, we now have some treatment modalities to prevent the onset of preterm labor. In spite of them, the incidence of preterm labor is 5–12%, which has not decreased over the last several decades in each country.

This book covers various aspects of preterm labor and delivery such as its current statistical status, background pathophysiology, prevention and treatments, neonatal problems, placental pathology, and so on. Some topics are also provided considering Japan's specific situation, including long-term tocolysis and long-term antibiotics for premature rupture of the membranes, for example. Hopefully, this book will enable all the obstetric caregivers to understand preterm labor from its basic scientific background to the current clinical managements. In addition, young clinician scientists should be aware of the facts that many fields in preterm labor and delivery need to be investigated to further improve their outcome.

Miyazaki, Japan
May 2019

Hiroshi Sameshima, M.D., Ph.D.

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Part I

Preterm Labor: A Challenge

Impacts on Perinatal Ecology

1

Tsuyomu Ikenoue

Abstract

Preterm labor is an important clinical entity in perinatal medicine. To apply ecology model to preterm labor is useful to make a framework for organizing medical care and education.

Keywords

Medical ecology · Preterm · Population-based study

Preterm labor and delivery has been one of the major problems to be solved in the modern obstetrics. The incidence of preterm delivery (<37 weeks of gestation) is only 6% in some developed countries including Japan. However, it accounts for 90% of perinatal mortality and 60% of perinatal brain damage [1, 2]. Preterm delivery is not just a problem of timing (an early onset of labor contractions), but is recognized as a syndrome associated with systematic disorders including inflammation.

Here some questions arise regarding how we can manage preterm labor to improve infant's outcome or what the best framework is to care these high-risk women in varying socio-economical condition.

To answer these medical questions in general, the ecology model was firstly introduced to the medical sciences in 1961 [3, 4]. This model has been extremely useful to provide a framework for organizing medical care and medical education. Since then, this model has been widely applied to many clinical fields and shown its usefulness over four decades [3, 4]. We thus applied the general concept of

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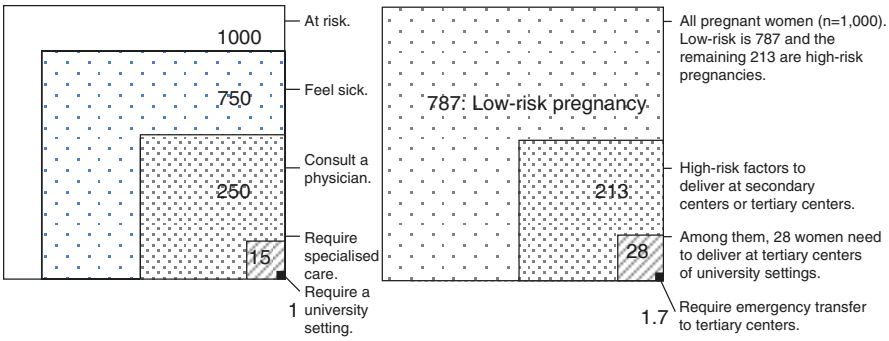

Lt.) The original ecology model of medical care.

Rt.) Applying ecology model for obstetric care.

Fig. 1.1 Applying the medical ecology model to perinatal medicine. Left figure (Lt.) shows the original ecology model of medical care by White KL. Among the 1000 adults at risk, 750 of them feel sick, 250 consult a physician, 15 require specialized care, and one needs to be referred to a university setting medical center. Right figure (Rt.) shows the results of our regional population-based study. Among the 1000 pregnancies, 787 women are "low-risk" pregnancy and the remaining 213 have some high-risk factors. Among these 213 women, 28 women (about 3% of the total pregnancies) need tertiary center care of university settings, and 1.7 women require emergency transfer to a university setting. Both figures have remarkable similarity

medical ecology to the specific field of perinatal medicine in southern part of Japan by using our regional population-based field study, where perinatal mortality is the world lowest (<4.0/1000 deliveries) and perinatal database has been established for 20 years [1, 2]. Figure 1.1 comparatively shows the similarities and differences between the original ecology model for primary medicine and one applied to perinatal medicine, which we found remarkable similarity [5]. These results imply that the original ecology model can be applied to perinatal medicine in that 25% of pregnancies having high-risk factors would be well managed at high-level perinatal centers (secondary or tertiary perinatal centers) and that the remaining 75% women having low-risk pregnancies could be managed by primary hospitals.

Among the high-risk factors to be delivered at high-level perinatal centers, two-thirds are complicated by threatened preterm labor or preterm premature rupture of the membranes, leading to preterm delivery. Therefore, preterm labor and delivery is also the leading cause from the viewpoint of medical ecology in obstetrics. In other words, women having preterm labor should also be managed in the framework following the ecology model of obstetrics. The most high-risk women at <28 weeks of gestation, for example, need to give birth at a tertiary perinatal center of university level settings. On the other hand, moderately high-risk women with clinical manifestations of preterm labor at 28–32 weeks of gestation, for example, can deliver at secondary centers. To make a functional framework by using the ecology model for perinatal medicine is beneficial for premature infants as well as medical teams.

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Definition and Diagnosis of Preterm Labor

2

Hiroshi Sameshima

Abstract

Preterm birth is the leading cause of neonatal mortality and morbidity, as well as the most common reason for antenatal maternal hospitalization. Preterm labor is defined as regular uterine contractions associated with cervical changes (cervical dilatation ≥2 cm and effacement) that start before 37 weeks of gestation. However, the diagnosis of threatened preterm labor is imprecise to identify women who will give birth preterm infants in near future. In the last few decades, more subjective parameters are used, which include cervical length measured by transvaginal ultrasonography, fetal fibronectin concentrations of the cervicovaginal secretions, and the combination of the two tests. Prospective studies show that shorter cervical length (15–30 mm or less) is significantly associated with spontaneous preterm delivery. Systematic reviews show that fetal fibronectin measurement combined with shorter cervical length has a high negative predictive value (>98%) for delivery within 7 days but a low positive predictive value (30–50%). The prenatal caregivers should take full advantage of the high negative predictive value of the combined test for women with threatened preterm birth.

Keywords

Preterm birth · Cervical dilatation · Cervical length · Fibronectin · Uterine contractions

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2.1 Introduction

Preterm birth is the leading cause of neonatal mortality and morbidity in the developed countries. Preterm labor is also the most common reason for antenatal hospitalization of pregnant women, which is associated with socio-economical burdens to the society. Therefore, the diagnosis of threatened preterm labor, which will result in preterm birth, and the managements of preterm labor are important. However, early diagnosis of true preterm labor is difficult because the differentiation between the true labor and false labor is not clear until there are detectable changes in cervical maturation of the uterus, which, in turn, might be too late to start some treatments to prolong pregnancies. In this chapter we will discuss the current status of the definition of "preterm," trends of preterm birth, and the definition of preterm labor.

2.2 Gestational Weeks Corresponding to Preterm Birth

Preterm birth is defined according to the gestational age at birth (Table 2.1). Gestational age at birth is divided into four categories: abortion, preterm, term, and postterm. Preterm birth is then subdivided into late preterm, early preterm, and extreme preterm.

The duration corresponding to "late preterm" was classically called "near term," in which we expected that those infants born at 34–36 weeks of gestation are considerably well matured, close to the term infants, from the developmental viewpoint. However, because of the recent recognition that late preterm infants have significantly higher incidences of infant's short-term and long-term morbidity compared to those of the term infants, the new term "late preterm" has now been widely accepted.

Table 2.1 Definition of preterm birth according to gestational age

Gestational age at delivery (weeks)		
≤21	Abortion	
22–27	*Preterm*	Extreme preterm
28		
29		Early preterm
30		
31		
32		
33		
34		Late preterm
35		
36		
37	Term	
38		
39		
40		
41		
≥42	Postterm	

According to the recent definition, "late preterm" is from 34 + 0/7 weeks until 36 + 6/7 weeks and "early preterm" is before 34 completed weeks. In addition, those who are delivered before 28 completed weeks are commonly named as "extreme preterm."

2.3 Trends in Preterm Birth

Preterm birth occurs at or after 22 weeks of gestation, and until 36 completed weeks of gestation (Table 2.1). The rate of preterm birth in Japan has a tendency of increasing from 4.1% in 1980 to 5.4% in 2005, and is relatively stable over a decade until 2010 (5.7%) (Fig. 2.1) [1]. Thereafter, the percentage of preterm birth started decreasing to 5.6% in 2015. Whether this decreasing trend is real needs to be determined.

The preterm birth rate is different among the districts in Japan. For example, a regional population-based study in a rural part of southern Japan, which has a population of one million and 10,000 deliveries per year, shows that the percentage of preterm birth is still gradually increasing from 5.9% in 2005 to 6.7% in 2012 (Fig. 2.2) [2]. In that study, the rate of low birthweight infants has also been increasing from 10% in 2005–2006 to 10.5% in 2011–2012 [2].

A similar trend in preterm birth rate is reported in America, in which it increased from 9.4% in 1984 to a maximum of 12.8% in 2006, and then started decreasing to 11.7% in 2011 [3].

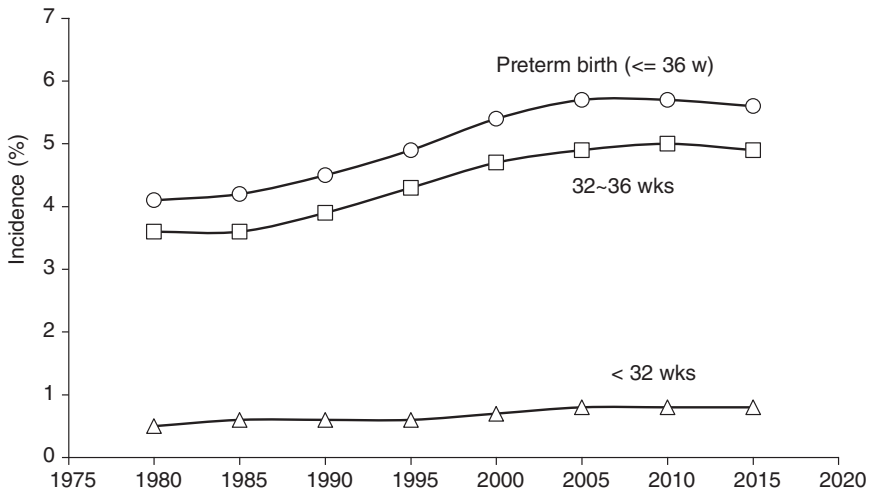

Fig. 2.1 Japan's trends in preterm birth rate from 1980 to 2015. Temporal changes in preterm birth rate in Japan are depicted. Open circles represent total preterm birth (≤36 weeks of gestation), squares represent 32–36 weeks of gestation, and triangles represent <32 weeks of gestation

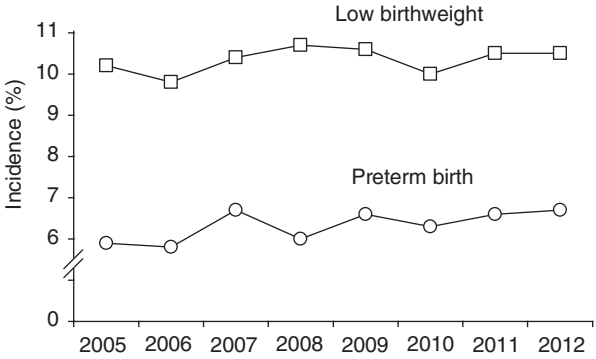

Fig. 2.2 Preterm birth rate from a regional population-based study in southern Japan. Temporal changes in preterm birth rate in one district of the southern Japan are depicted. Open squares represent low birthweight rate and circles represent preterm birth rate

2.4 Definition of Preterm

Preterm labor is diagnosed by clinical manifestations and medical examinations, which include both uterine activity and cervical maturational changes of the uterus. Thus, preterm labor is defined as regular uterine contractions associated with cervical changes that start before 37 weeks of gestation. Uterine activity alone can be misleading because of the presence of false labor, which is spontaneous uterine contractions alone. Some women who deliver preterm have uterine contractions that is attributed to false labor, causing difficulties in differentiating true labor from false labor. Maturational changes in the uterine cervix include effacement and dilatation.

Until recently in Japan, the definition of preterm labor was either regular uterine contractions or demonstrable changes in cervical dilatation and effacement. Because of the disparities from the international definition of preterm labor, our society has changed its definition in 2017, in which it requires both regular uterine contractions and cervical changes [4]. In addition, since preterm birth includes women with cervical incompetence, a woman who has cervical dilatation ≥2 cm at her first visit is also diagnosed as preterm labor [4]. The impact of the definition changes on preterm birth rate in Japan needs to be investigated.

2.4.1 Clinical Signs

Identifying women who will give birth preterm infants is an inexact process. The signs and symptoms of preterm labor that pregnant women may have are as follows: changes in vaginal discharge (especially bloody or watery one), pelvic or lower abdominal pressure, dull backache, and regular uterine tightening or contractions. These clinical signs are subjective, nonspecific to preterm labor, and also present in some normal pregnancies, therefore lacking precision.

The importance of these signs as a premonitory sign for preterm birth has been proposed. A prospective observational study was conducted in 690 women in Texas who had clinical signs of preterm labor with intact membranes (cervical dilatation <2 cm) between 24 and 33 weeks of gestation, but did not have cervical changes over the 2-h observation period [5]. Comparisons with the general obstetric population revealed that incidence early preterm birth <34 weeks of gestation was similar (2% compared with 1%, not significant), but that of late preterm birth (34–36 weeks of gestation) was significantly higher (5% compared with 2%, $p < 0.01$). This study suggested that some women with clinical manifestations alone may become targets of managing preterm labor to decrease the incidence of late preterm birth. Further large-scale, prospective studies are required. We should also take it into consideration that there are some differences in the incidence of preterm birth according to the racial and ethnical groups.

Unfortunately, uterine contractions combined with cervical changes do not reliably predict preterm labor, either. The abovementioned prospective observational study also showed that only 27% of women delivered preterm who had had contractions with progressive cervical dilatation before 34 weeks of gestation [5]. In other words, 73% of women having clinical signs of threatened preterm labor resulted in term delivery. Similar trends have also been reported in other prospective cohort studies [6]. Among the 9% of 2534 low-risk pregnancies, who were diagnosed as having threatened preterm labor, only 38% resulted in preterm delivery (Fig. 2.3). Again, the diagnosis of threatened preterm birth is an imprecise and problematic process. We conclude that the large majority of women who experience symptoms of preterm labor will not deliver preterm and more than half will deliver term.

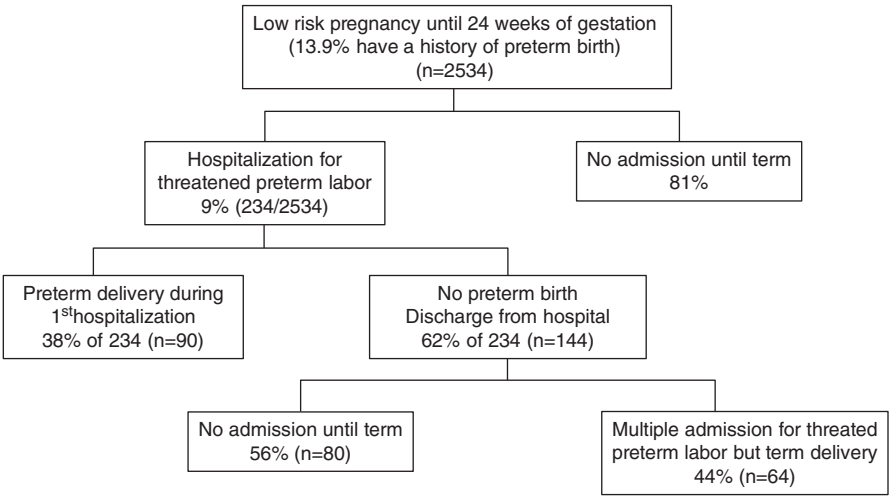

Fig. 2.3 Preterm birth rate among 2534 low-risk pregnancies: A prospective cohort study. A prospective cohort study using 2534 women shows 9% of them need hospitalization for threatened preterm labor. Among them, only 38% resulted in preterm delivery and the remaining 62% delivered at term

2.4.2 Cervical Changes

Cervical dilatation ≥2 cm with uterine contractions is a predictor of preterm birth. Similarly, asymptomatic cervical dilatation ≥2 cm after mid-pregnancy is also suspected to be a risk factor for preterm delivery, but that is still controversial. Parous women sometimes have asymptomatic cervical dilatation ≥2 cm during second trimester and result in term delivery.

Cervical length is measured by transvaginal ultrasonography between the internal os and the external os (Fig. 2.4, normal cervical length in left and shortened cervical length in right) [7]. Some education and cautions are required for the standardization of cervical length measurements [7, 8]. Anatomic pitfalls include undeveloped lower uterine segment (especially before 18 weeks of gestation), focal myometrium contraction, and endocervical polyp, which may cause misinterpretation of cervical length. Technical pitfalls include incorrect interpretation of the internal os by disoriented placement of vaginal probe. Therefore, cervical length should be measured by experienced operators.

The first prospective, multicenter study was published in 1996 [7], in which cervical length was measured in 2915 low-risk women at approximately 24 weeks and again at 28 weeks of gestation to see prospectively the relationship between the cervical length and the incidence of preterm delivery. Cervical length was 35 ± 8 mm at 24 weeks and 34 ± 9 mm at 28 weeks of gestation (mean ± SD). They found that the risk of spontaneous preterm delivery is increased as the cervical length decreased. Following this prospective study, cervical assessment has been evaluated extensively and shorter cervical length (<25 mm at approximately 24 weeks of gestation) and dilatation of the internal os have been used as predictors for preterm delivery (Fig. 2.4).

A multicenter, prospective study was also conducted in Japan using 1365 pregnant women [9]. They showed that the average cervical length at approximately 20–24 weeks of gestation was 43 ± 8 mm for nulliparous and 38 ± 10 mm for parous

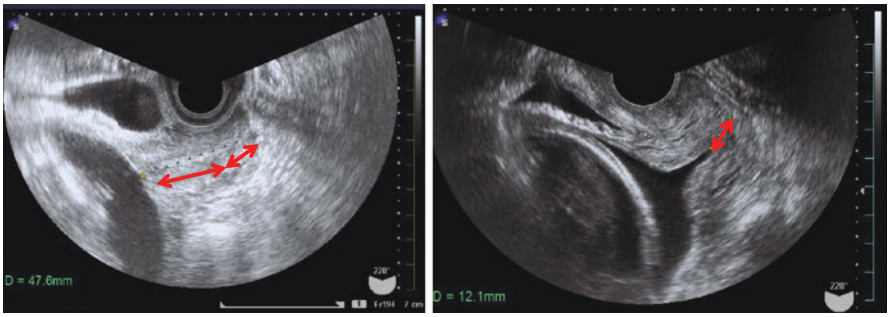

Fig. 2.4 Cervical length measured by transvaginal ultrasonography. The right picture shows normal ultrasonographic pattern of the uterine cervix. Both the internal os and external os, and the cervical canal are visualized. The cervical length is measured by adding the 2 arrow-bar lengths. The left picture shows cervical shortening (length is 12.1 mm) and protrusion of the amniotic sac into the endocervical canal to make a "funneling" shape

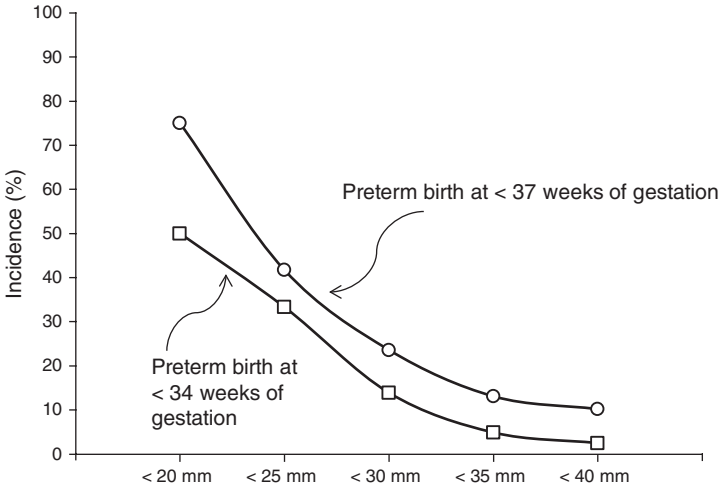

Fig. 2.5 Preterm birth rate according to the cervical length at 20–24 weeks of gestation. Preterm birth rates are depicted as a function of cervical length in Japanese population. Open circles represent preterm birth rate <37 weeks of gestation and squares represent preterm birth rate <34 weeks of gestation. Preterm birth rate increases as the cervical length shortens. (Modified from reference [9] by Shiozaki et al.)

women (mean ± SD). They also showed that preterm birth rate increased with the progression of cervical shortening as shown in Fig. 2.5. For example, 42% of women with cervical length <25 mm delivered preterm (at <37 weeks of gestation) and 75% of women with cervical length <20 mm delivered preterm.

2.4.3 Biomarkers for Preterm Birth: Fibronectin

As mentioned, since the physical markers of preterm labor are inaccurate, various chemical methods to help predict preterm birth have been assessed. At present, one of the promising markers is fibronectin [10–13]. Fetal fibronectin is a glycoprotein localized at the chorio-decidual interface, which is released into the cervico-vaginal secretions by the stimulation of uterine contractions. It appears to reflect stromal remodeling of the uterine cervix toward cervical maturation.

The combination of cervical length and fibronectin testing has been extensively investigated [10–13], which shows a high negative predictive value (>98%) for delivery within 7 days and a low positive predictive value (Table 2.2) [11]. The current strategy for the best use of this combined test is to take full advantage of its high negative predictive value of fibronectin testing for women having a shorter cervical length of <15 to 30 mm. Namely, even though a pregnant woman has shorter cervical length, the risk of preterm birth <7 days is low as long as the fibronectin value is low. This approach could reduce the number of unnecessary referral cases of threatened preterm labor.

Table 2.2 Screening efficacy of the combined test for prediction of preterm delivery

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<37 weeks of gestation	36.4	83.0	49.4	74.4
<34 weeks of gestation	53.8	84.3	36.8	91.5
<7 days	71.4	96.8	45.4	98.9

Cervical length cutoff points <30 mm and <15 mm are included
Fibronectin cutoff point is >50 ng/mL
PPV positive predictive value, *NPV* negative predictive value
Modified from reference [11]

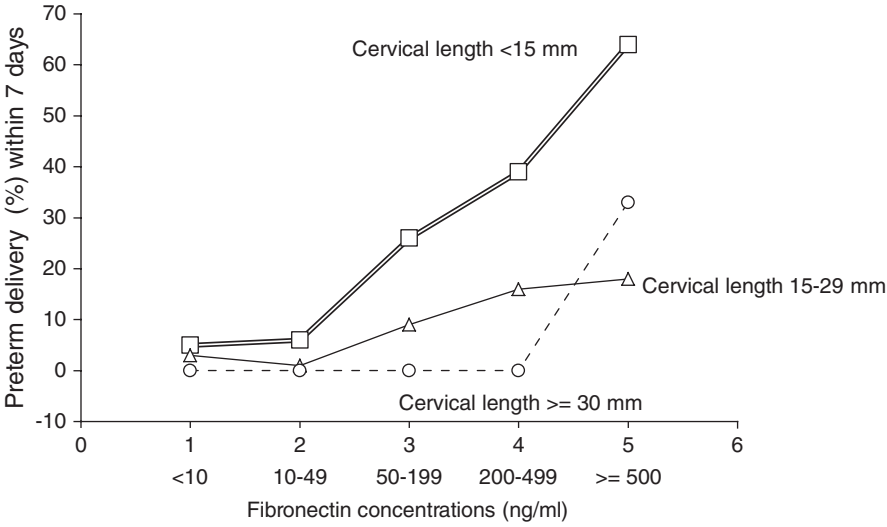

Fig. 2.6 Preterm delivery rate within 7 days with the combined tests (quantitative fibronectin and cervical length). Preterm delivery rate within 7 days is depicted as a function of fibronectin concentrations. Open circles with double-solid-line represent women with cervical length <15 mm, which have higher preterm delivery rate compared with those with cervical length 15–29 mm (triangles and solid line) and those with cervical length ≥30 mm (circles and dotted line). In addition, within the cervical length group, preterm delivery rate increases as the fibronectin concentration increases

Recently, quantitative fetal fibronectin measurement has been used in combination with cervical length for predicting preterm labor within 7 days [13]. As shown in Fig. 2.6, the shorter the cervical length, the higher the incidence of preterm birth within 7 days occurs in any fibronectin concentration groups. In addition, in any cervical length group, the preterm delivery rate increases proportionally as the fibronectin concentrations increase. They concluded that quantitative fibronectin testing alone is as effective as the conventional combined tests (qualitative fibronectin testing with cervical length) [13]. Thus, combined tests with quantitative fibronectin and cervical length may have better performance to predict preterm delivery within 7 days.

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Epidemiology and Incidence of Preterm Delivery

3

Junji Onishi

Abstract

Definition of premature birth is a delivery that occurs less than 37 weeks gestation. However, the initial number of gestational weeks recorded as statistics varies from region to country. In the world, about 15 million preterm infants are born every year only by knowing statistically. Premature birth is the most important cause of increasing neonatal morbidity and mortality. The cause of premature birth is two-thirds naturally occur, and one-third is caused by a medical factor. The reason for this reduction is related to the development of public health and preventive medicine as clarification of risk factors and mechanisms causing preterm birth has progressed. The risk of premature infant morbidity and mortality increases in inverse proportion to the number of gestational weeks. Premature birth is associated with 75% of perinatal death and accounts for 50% of the cause of long-term morbidity. Respiratory disorders such as respiratory distress syndrome are representative as short-term risk of preterm infants. As immaturity further increases, in premature infants, disorders of the brain nervous system and circulatory system also occur and are exposed to the risk of systemic infection. On the other hand, a risk of preterm infants over the long term, the possibility of abnormality in growth and neurological development must also be considered. This suggests that diseases of premature birth will continue to affect the medical economy over the long term.

Keywords

Epidemiology · Medical economy · Maternal environment · Public health

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3.1 Introduction

Definition of premature birth is a delivery that occurs less than 37 weeks gestation [1]. However, the initial number of gestational weeks recorded as statistics varies from region to country. Premature birth is the most important cause of increasing neonatal morbidity and mortality. The cause of premature birth is two-thirds naturally occur, and one-third is caused by a medical factor. The majority of medical causes are hypertensive disorders of pregnancy and fetal growth restriction [2]. In the world, about 15 million preterm infants are born every year only by knowing statistically [3]. In many industrialized countries, preterm birth had increased until around 2005, but it has declined slightly in recent years. In the USA, it was 12.7% in 2007, but it decreased to 11.4% in 2013 [4]. The reason for this reduction is related to the development of public health and preventive medicine as clarification of risk factors and mechanisms causing preterm birth has progressed. The risk of premature infant morbidity and mortality increases in inverse proportion to the number of gestational weeks [5]. Premature birth is associated with 75% of perinatal death and accounts for 50% of the cause of long-term morbidity [6]. Respiratory disorders such as respiratory distress syndrome are representative as short-term risk of preterm infants. Furthermore, if immaturity increases, brain damage such as periventricular leukomalacia and intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, etc. are caused. Also, in the long-term premature infants, the risk of retinopathy of prematurity and chronic lung disease increases. In preterm infants, they are exposed to high concentration oxygen environments and infections, so the risk of retinopathy of prematurity and chronic lung disease increases. As a risk of preterm infants over the long term, the possibility of abnormality in growth and neurological development must also be considered. This suggests that diseases of premature birth will continue to affect the medical economy over the long term.

3.2 Epidemiology of Preterm Delivery

Premature birth is largely divided into three categories. One is that the termination becomes earlier due to maternal or fetal diseases, and is carried out by cesarean delivery before artificial labor induction and labor pains are started. Next, it is due to the spontaneous labor that has not been premature rupture of the membranes. Lastly, it is deliveries by vaginal or cesarean section after premature rupture of the membranes. Approximately 30–35% of premature birth is due to medical indication, about 40–45% is due to spontaneous labor, and about 25–30% is due to premature rupture of the membranes [7]. The frequency of premature rupture of the membranes causing spontaneous premature deliveries varies among races. In general, whites are preterm deliveries caused by labor without premature rupture of the membranes, but blacks are prematurely bred after premature rupture of the membranes [8]. Also, premature birth has a different frequency even in gestational weeks. The frequency at pregnancy less than 28 weeks is about 5%, 9.5% at 28–31 weeks gestation, 12.1% at 32–33 weeks gestation, and about 71.3% at

pregnancy 34–36 [9]. Increased preterm birth rate in single gestation can be explained by an increase due to medical indication. The increase in preterm birth in multiple gestations is thought to be a major involvement in the development of reproductive medicine. Singleton after IVF-ET will also increase preterm birth. Premature rupture of the membranes refers to rupture of less than 37 weeks gestation that occurred more than 1 h prior to onset of uterine contraction. The cause of premature rupture of the membranes in many cases is unknown. However, asymptomatic intrauterine infection often causes early rupture. Risk factors of rupture membranes are not different from preterm birth without rupture; infection diseases and smoking occupy an important part. Normally, the fetal membrane becomes a barrier to prevent infection into the uterus. However, after rupture, it usually develops into intrauterine infection and labor.

3.3 Incidence of Preterm Delivery

Premature birth occurs from various causes. Preterm delivery exhibits various symptoms, eventually accompanied by progressive cervical ripening to regular uterine contractions; delivery takes place in less than 37 weeks after progress of labor. In the USA, the premature birth rate has increased by about 36% from 9.4% in 1984 to 12% in 2006 [10]. However, the rate of premature birth has started to decline after 2006, and it is 11.4% in 2013 [4, 11]. Regarding the decline in the premature birth rate, premature births of less than 34 weeks gestation are also permitted in both pregnancies, 35–36 weeks called late preterm. Despite the declining trend of preterm birth in recent years, the incidence rate is higher than in the 1980s and 1990s. The preterm birth rate in Japan also increased steadily from the 1980s to the 2000s, but it has shown a slight declining trend in the 2010s. Perinatal outcome prognosis has been remarkably improved by improvement of medical technology in recent years. However, contrary to advances in technology, the premature birth rate has not received much of this benefit. It is presumed that various factors such as changes in women's lifestyle habits and aging of pregnancy age are related to the cause, but on the other hand preterm delivery is still unsolved in current perinatal medicine It can be said that there is.

3.4 Epidemiological Risk Factor of Preterm Delivery

Today, premature birth is considered a syndrome that is located in many developmental mechanisms including infection and inflammation, utero-placental circulation failure, bleeding, uterine overdistension, stress, other immunologic medical mechanisms. An increase in the number of risk factors for premature birth is considered to be related to the cause of a transition from a state without uterine contraction to a direction of labor and premature rupture. Many of the risk factors for preterm birth are thought to activate infection and inflammatory pathways leading to a systemic inflammatory state. Therefore, determination of risk factors for the prediction of premature birth is important.

Many of the epidemiologic factors are greatly influenced by the economic level of the country in which the pregnant woman lives, such as young pregnancy, elderly pregnancy, diet, low educational background, and low income. Factors in lifestyle and daily life include smoking, drug addiction, housing environment, hard labor, stress, and the like. Obstetric factors include *grand multipara* (over 5 para), multiple pregnancies, and a history of abortion, a history of *cervical incompetency*, and a history of premature birth. The organic factors of the uterus are famous for uterine malformations and fibroids. Maternal complications also affect premature birth. Typical diseases include hypertension, diabetes, chronic inflammatory diseases, and the like.

3.4.1 Social Environment (Economy, Race, Ethnicity, etc.) and Preterm Delivery

Worldwide, many of the premature births occur in economically poor third world countries, and it is believed that most of the causes are caused by systemic infections such as malaria, HIV, tuberculosis, and intestinal parasites [12]. In these countries, using a cost-effective approach in recent years has increased prevention and treatment of premature birth defects where little progress has been made in the past 50 years, but the effect. As the country develops economically, the medical industry also grows rapidly. Rapid development of the medical industry also affects perinatal medicine. Medical intervention for pregnancy leads to an increase in artificial premature birth. Therefore, the preterm labor rate is characterized by interlocking with the cesarean section rate. In 2005, Barros et al. reported that the cesarean section rate increased eight times in Brazil over the past 20 years, and the incidence of preterm birth increased three times [13].

Distribution status of premature birth in the USA is different for race and ethnicity. Regarding the newborn mortality rate in the USA in 2009, 77% of those related to race and ethnicity result from preterm birth [10]. It is obvious that this is an epidemiological view that low-income and low-living environments affect preterm delivery. The rate of premature birth in the USA is higher than in other developed countries, such as Canada, but it is also related to race and ethnic diversity [14]. In the USA and the UK, it is reported that women classified as blacks, African Americans, and African Caribbean are always at high risk of premature birth. The rate of premature birth is 16–18% for black women, while 5–9% for white women. For black women, the frequency of premature birth at a very early stage is 3–4 times higher than that of other races and tribes [15, 16]. The divergence of the preterm rate among the USA and other countries probably is due to the high rate of premature birth of the black population in the USA. The imbalance in the rate of premature birth between black women and white women remains universal and unexplainable in many cases. However, that imbalance may contribute to some reproductive advantage. East Asians and Hispanics have few premature births as features. South Asian women, including sub-continents like India, have a high frequency of low birth weight infants associated with fetal growth restriction, but no increase in premature birth.

Regarding pregnant mothers, other demographic characteristics are low socioeconomic or low educational environmental conditions, young or aged pregnancy, unmarried [17, 18]. However, it is not clear how mothers' demographic characteristics are related to premature birth.

Observational studies on types of work and physical activity related to preterm birth have not resulted in a clear increase. However, research on risks related to work varies depending on various factors. However, if each work condition is adjusted, long-term work under stress and responsible hard labor are probably related to an increase in premature birth. The degree of physical activity is unknown related to premature birth. Regarding the population of immigrants in the USA, it is known that the longer the period of life in the USA, the higher the preterm rate, but the cause is unknown.

3.4.2 Maternal Nutritional Status and Preterm Delivery

Many mechanisms are conceivable for the influence of pregnant women's nutritional status on premature birth. Among them, the nutritional status of pregnant women is strongly influenced by the economic condition of the living area. Nutritional status during pregnancy can be objectively evaluated by body mass index, nutritional intake, blood biochemical test, etc. [19, 20]. For example, if a pregnant woman has a low BMI during pregnancy, the pregnant woman will inhibit the tendency to become obese, but there is a high risk of natural premature birth. If pregnant women have less serum iron, folic acid, and zinc, they are more premature delivery than pregnant women in normal range [21]. Extreme leanness and obesity of mothers cause premature birth. The maternal weight loss causes a decrease in circulating blood volume and uterine blood flow in pregnant women, which can also cause natural premature birth. A thin pregnant woman is deficient in vitamins and minerals, and its deficiency increases blood flow reduction and maternal infection. On the other hand, obesity pregnant women have a higher incidence of congenital malformations such as neural tube defects, but these newborns are often preterm infants. In addition, obese pregnant women tend to be preeclampsia and gestational diabetes, and their complications may cause premature birth.

3.4.3 Preterm Delivery and Risk of Recurrence

Risk of recurrence of premature birth is reported to be around 30% in review by systematic review and meta-analysis [22]. The recurrence rate did not significantly differ between randomized controlled trials and cohort studies. The risk of recurrence of premature birth is also affected when premature birth is repeated or when premature birth weeks are early. In pregnant women whose previous delivery was preterm labor, the risk of premature birth of the next pregnancy is 2.5 times higher [23]. On the other hand, the relationship with pregnancy week number of preterm

birth is also important. Although the mechanism by which premature birth is repeated is unknown, a woman with spontaneous premature delivery at the early gestation week tends to be preterm birth the next pregnancy. Even if time has not passed since the last delivery, it raises the risk of premature birth. If this pregnancy is less than 6 months between the previous pregnancy, the risk of preterm birth doubles in this pregnancy [24]. Therefore, a woman with a history of premature birth has a shorter pregnancy period the next time compared with a woman who has delivered in term delivery. Although the mechanism is not clear, it is thought that as a supported idea, it takes time for the uterus to return to a normal state, including the elimination of the inflammatory state that was merged with the previous pregnancy. Intrauterine infections of latency and antibiotic resistance are probably responsible for repeated premature births. The problem underlying the cause of premature birth may be chronic diseases such as diabetes, hypertension, obesity, and sustained inflammatory diseases.

3.4.4 Multiple Pregnancy and Preterm Delivery

Multiple pregnancies account for only 2–3% of all pregnancies, but they are important as causes of premature birth, causing 15–20% of all premature births. Multiple pregnancies are increasing due to advances in assisted reproductive technology in recent years. About twin pregnancies, premature birth accounts for about 60%. Excessive progress of the uterine body is thought to cause uterine contraction and premature rupture of the membranes, which causes an increase in natural preterm delivery. About 40% of twins become natural labor pain or premature rupture before 37 weeks gestation. Other premature birth causes in twins are preeclampsia and other maternal or fetal abnormalities.

3.4.5 Environmental Stress and Preterm Delivery

In mothers who have experienced high levels of stress psychologically and socially, even after adjusting social demographics, medicine, behavioral hazards effects, the frequency of premature birth is generally less than twice, but it increases [25, 26]. Therefore, if exposed to a state that is objectively satisfied with stress objectively like instability of the housing environment and severe maternal poverty, it tends to be preterm birth. The mechanism of increasing premature birth under the cooperation of psychology and society is not clear, but the role of corticotropin releasing hormone has been proposed [27–29]. Women who are exposed to stressful conditions are also found to have elevated blood in inflammatory markers (such as CRP). From the relationship between stress and inflammatory markers, it is suggested that systemic inflammation occupies an important role of pathway that stress increases preterm delivery.

3.4.6 Pleasure Products (Smoking, Alcohol, and Drugs) and Preterm Delivery

Approximately 20–25% of pregnant women smoke in the USA, of which 12–15% of pregnant women smoke throughout pregnancy [30, 31]. Tobacco will increase the risk of premature birth (less than 2 times) even if other effects are adjusted. However, it is not clear how smoking is related to premature birth. Tobacco's smoke contains over 3000 chemical substances, but the influence of most of it is unknown. However, as both nicotine and carbon monoxide are potent vasoconstrictors, it is thought to cause direct damage to the placenta and decrease the blood flow in the uterus and placenta. Both placenta damage and blood flow reduction can be retardation of intrauterine fetal development or preterm birth [32]. Smoking is also associated with systemic inflammation, which can also be preterm from the pathway [33]. Mild or moderate alcohol intake does not increase preterm delivery, but taking too much alcohol can cause preterm birth [34]. It is suggested that the use of cocaine and heroin is also premature in some studies [35].

3.4.7 Preterm Birth and Epidemiology

Children born at less than 37 weeks gestation have more morbidity due to immaturity in each organ than in infants born in full term. In the past 40 years, the complications of infants born in less than 34 weeks were due to immaturity [36]. Increased morbidity of late preterm infants from 34 to 36 weeks has been noted since 2005 [37]. Among preterm infants, low birth weight children weighing less than 1500 g have many problems that have not yet been resolved. These very low birth weight infants cause not only medical complications associated with immaturity but also long-term linkage such as nerve development disorder. In Japan, gestational age after 22 weeks of pregnancy is premature birth, and the prognosis with birth weight is poor as the body weight is smaller [38, 39]. Neonatal death of premature infant is thought to have a boundary at about 28 weeks. If the birth weight is 1000 g or more, or if the number of births reaches 28 weeks or more in girls and 30 weeks or more in boys, the survival rate exceeds 95% [40]. The premature infant's medical care is expected to cost from its morbidity. In the USA, the cost of preterm birth was $26.2 billion in 2006 as of 2006 and the cost of one premature infant was $ 51,000 [41].

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Part II

Preterm Labor and Intrauterine Infection and Inflammation

Subclinical Intrauterine Infection

4

Noriko Yoneda, Satoshi Yoneda, Hideki Niimi, Isao Kitajima, and Shigeru Saito

Abstract

Intrauterine (intra-amniotic) infection is recognized as the leading cause of preterm delivery, and is a major cause of a poor neonatal prognosis worldwide.

Maternal clinical chorioamnionitis (CAM), characterized by maternal fever, tachycardia, uterine tenderness, and leukocytosis, has been implicated in extremely and very preterm deliveries as well as a poor neonatal prognosis such as early-onset neonatal sepsis and necrotizing enterocolitis. Many cases of preterm birth with or without clinical CAM show intrauterine inflammation (histological CAM). Further clarification of the relationship between intrauterine infection and inflammation may contribute to the development of novel therapeutic strategies.

Approximately 30% of idiopathic preterm labor cases have been linked to subclinical intrauterine infection; however, inflammation associated with subclinical infection is difficult to detect using a peripheral blood analysis. Recent studies showed that amniotic fluid (AF) is very useful material for evaluating intra-amniotic infection and inflammation. The detection rate of microorganisms in AF using a polymerase chain reaction (PCR)-based methodology is higher

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than that with a standard microbial culture system. By using highly sensitive and reliable PCR, polymicrobial infections with *Mycoplasma*/*Ureaplasma* and other bacteria were shown to induce severe intrauterine inflammation associated with a poor perinatal prognosis in preterm labor. Appropriate antibiotic therapy for PCR-positive preterm labor cases may prolong the gestational period. Furthermore, a PCR analysis showed that AF sludge reflects intra-amniotic inflammation with or without microorganisms.

In this section, we discussed subclinical intrauterine infections detected using highly sensitive and reliable PCR as well as an IL-8 analysis of AF.

Keywords

Amniotic fluid "sludge" · Interleukin-8 (IL-8) · Intrauterine infection · Intrauterine inflammation · Polymerase chain reaction (PCR)

4.1 Introduction

Microbial invasion of the amniotic cavity is detected in 20–60% of cases of preterm labor (PTL) at <28 weeks' gestation and 10–25% of those at 28–32 weeks' gestation [1–3]. Intrauterine (intra-amniotic) infection and inflammation are the main causes of PTL with intact fetal membranes, particularly in extremely and very preterm deliveries [4].

Chorioamnionitis (CAM) is a common cause of preterm births and is often associated with fetal inflammatory response syndrome (FIRS). FIRS is characterized by increased systemic inflammatory cytokine concentrations, fetal vasculitis, and funisitis [5].

The presence of histological CAM and maternal and/or neonatal infection after a preterm birth is considered to be evidence of subclinical intrauterine infection [6]. However, difficulties are associated with detecting subclinical intrauterine infection in PTL cases using a peripheral blood analysis [7].

Regarding the detection of subclinical intrauterine infection, amniotic fluid (AF) is very useful for evaluating intra-amniotic inflammation and infection. A bacterial culture of AF remains the "gold standard" and most specific test for the documentation of intra-amniotic inflammation, but is limited because it may take a few (3–7) days to obtain definitive results, which is too long to be clinically useful [8]. Although molecular microbiology techniques, such as a polymerase chain reaction (PCR), are rapid and highly sensitive, false positives have been reported due to contaminating bacterial DNA in *Taq* DNA polymerase being amplified by PCR (Fig. 4.1). Eukaryote-made thermostable DNA polymerase has been established in order to overcome this issue (Fig. 4.1) [9]. In the following section, we described intrauterine infection and sterilized inflammation in cases of PTL using this highly sensitive and reliable PCR system.

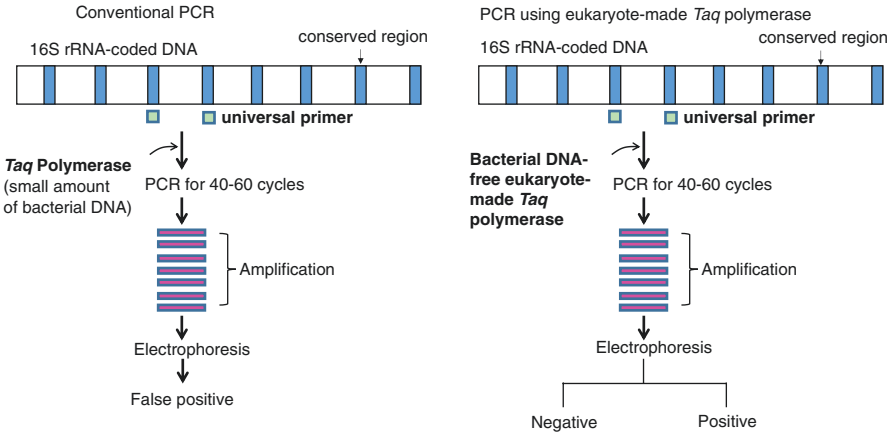

Fig. 4.1 Conventional PCR and PCR using eukaryote-made *Taq* polymerase

4.2 Detection of Microorganisms in AF by a Culture Method and PCR

The microbial cultivation method of AF is recognized as the "gold standard" for the detection of intrauterine infection; however, 1 week is needed to obtain results on possible infections by *Mycoplasma*, *Ureaplasma*, and other bacteria. Furthermore, difficulties are associated with detecting *Mycoplasma* and *Ureaplasma* using conventional cultivation systems. Molecular microbiology techniques, such as PCR, have emerged as rapid and highly sensitive methods for the detection of microorganisms including *Mycoplasma* and *Ureaplasma* in AF samples [10–18]. The detection rate of microorganisms in AF using a PCR-based methodology was previously reported to be higher than that by a standard microbial cultivation system [10, 11, 19–23]. The amniocentesis-to-delivery interval of PCR-positive culture-negative PTL cases was found to be significantly shorter than that of PCR-negative culture-negative cases, suggesting that PCR-positive culture-negative cases ($P = 0.03$) are pathogenic [24].

A quantitative real-time PCR assay for detecting bacteria is also important for assessing the load of microorganisms. High copy numbers of bacterial DNA have been reported in CAM stage III [25, 26], and the following 11 bacterial species are the dominant species of CAM stage III: *Ureaplasma parvum*, *Streptococcus agalactiae*, *Gardnerella vaginalis*, *S. anginosus*, *Sneathia sanguinegens*, *Eikenella corrodens*, *Prevotella bivia*, *Lactobacillus jensenii*, *Bacteroides fragilis*, *Porphyromonas endodontalis*, and *Mycoplasma hominis* [25]. Therefore, it is important to detect pathogenic microbes in AF.

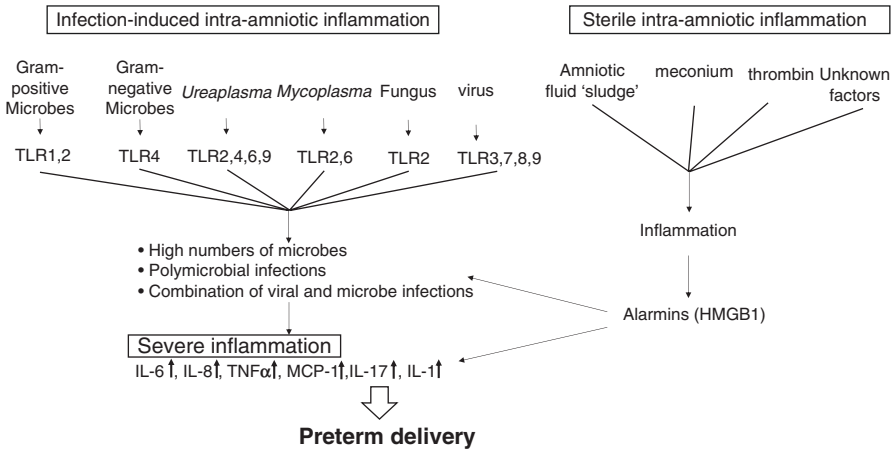

Fig. 4.2 Infection induced inflammation and sterile intra-amniotic inflammation in preterm delivery cases

4.3 Sterile Intra-Amniotic Inflammation and Micobial-associated Intra-Amniotic Inflammation in Preterm Delivery

Most intra-amniotic infections are subclinical in nature, and, thus, occur in the absence of clinical CAM. The most frequent microorganisms detected in AF are genital *Mycoplasma* [27–30], *Ureaplasma* species [31, 32], *Gardnerella vaginalis*, and *Fusobacteria* species. Polymicrobial invasion of the amniotic cavity is detected in approximately 30% of cases [23, 33].

Romero et al. previously proposed that intra-amniotic inflammation without detectable microbes is a mechanism of disease in PTL [2, 34, 35] based on elevations in the amniotic inflammatory mediators (interleukin (IL)-6 [2, 34, 35], IL-8 [36], matrix metalloproteinase 8 (MMP-8) [37], monocyte chemotactic protein-C (MCP-1) [38]), and other inflammatory markers (Fig. 4.2) [39]. Sterile intra-amniotic inflammation is more frequent than microbial-associated intra-amniotic inflammation [40], and we also showed that sterile intra-amniotic inflammation was common in PTL cases [41]. Therefore, infection and inflammation both need to be analyzed.

Damage-associated molecular patterns (DAMPs) are host biomolecules that initiate non-infectious inflammatory responses. Some alarmins, such as IL-1α [42, 43] and high mobility group box-1 (HMGB1) [44, 45], are elevated in the AF of patients with intra-amniotic inflammation (Fig. 4.2). Romero et al. reported an inflammatory-related protein network in spontaneous PTL. PTL cases with microbial-associated intra-amniotic inflammation had more coordinated AF inflammatory-related proteins than those with or without sterile intra-amniotic inflammation. These relationships were also stronger in patients with than in those without sterile intra-amniotic inflammation [46]. Therefore, sterile intra-amniotic inflammation is an important factor that induces preterm delivery. We previously reported that AF "sludge" is related to intra-amniotic inflammation with or without

microorganisms. AF "sludge" may be one of the factors that induces sterile intra-amniotic inflammation (Fig. 4.2) [41]. Meconium and thrombin also induce inflammation (Fig. 4.2).

4.4 Highly Sensitive and Reliable PCR Analysis of AF

PCR is useful for detecting microorganisms in AF; however, commercially available thermostable DNA polymerase (e.g., recombinant Taq polymerase) contains trace amounts of host (prokaryote)-derived bacterial DNA, which results in false positives when PCR cycles increase to improve sensitivity (Fig. 4.1) [22].

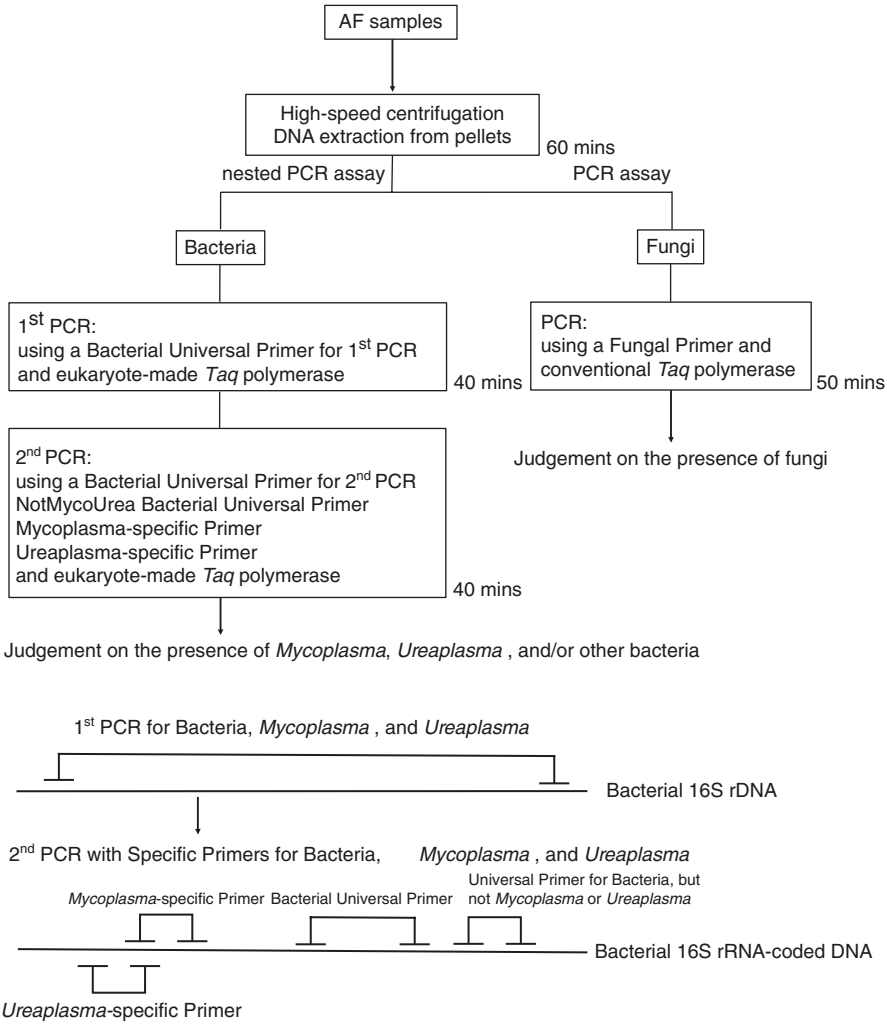

Fig. 4.3 Highly sensitive and reliable PCR method to detect microorganisms in amniotic fluid (AF) samples at the University of Toyama

In order to overcome this issue, a recent study reported a nested PCR-based method using eukaryote-made thermostable DNA polymerase, which is free of bacterial DNA contamination (Fig. 4.3) [9]. By using this eukaryote-made thermostable DNA polymerase, the highly sensitive and reliable detection of bacteria has become practicable. Regarding the detection of microorganisms in the AF of PTL cases, a method for detecting *Mycoplasma*, *Ureaplasma*, bacteria, and fungi using devised primer sets has been established (Fig. 4.3) [47].

This highly sensitive and reliable PCR method is useful for detecting intrauterine microorganisms. We previously reported that microorganisms were detected in the AF of 7.6% (9/118) of PTL cases using culture tests, and in 33% (39/118) of cases using the PCR method [24]. The PCR method is useful for detecting microorganisms that are difficult to culture and separate on conventional culture medium.

We also demonstrated that the amniocentesis-to-delivery interval of the culture (−) -PCR (+) group was significantly shorter than that of the culture (−) -PCR (−) group ($P = 0.03$) [24].

This finding suggested that viable but non-culturable microbes are pathogenic for PTD.

Previous studies reported that AF cytokines levels, such as IL-6 and IL-8, increased in PCR-positive culture-negative preterm delivery cases [10, 20, 23, 48]. Our findings also confirmed intrauterine inflammation in PCR-positive culture-negative cases.

Highly sensitive and reliable PCR showed that polymicrobial infections with *Mycoplasma*/*Ureaplasma* and other bacteria induced severe intrauterine inflammation associated with a poor perinatal prognosis in PTL (Fig. 4.1) [24]. In this case, multiple pathways of toll-like receptors (TLR) are activated, resulting in severe inflammation (Fig. 4.2). Severe inflammation is commonly observed in extremely preterm births.

4.5 AF Cytokine Levels

Previous studies described the evaluation of histological CAM using biological markers, such as maternal body temperature [49, 50], maternal white blood cell count (WBC) [49, 50], maternal C-reactive protein (CRP) [51–53], maternal or amniotic IL-6 [54–57], and amniotic IL-8 [58, 63].

IL-8 is a chemokine that is produced by a number of cell types, and proinflammatory markers have been reported in various diseases [59–61]. We demonstrated that IL-8 was an accurate marker for detecting the early stage of inflammation in the amnion. Our previous findings revealed that among amniotic IL-8, TNF-α, and IL-17 levels, those of IL-8 more clearly reflected each stage of h-CAM [62].

The cut-off value for amniotic IL-8 levels to predict the stage of h-CAM before delivery was assessed. Cut-off values for h-CAM were ≥9.9 ng/mL for stage I or higher, ≥17.3 ng/mL for stage II or higher, and ≥55.9 ng/mL for stage III. The sensitivities of predicting h-CAM of stage I or higher, stage II or higher, and stage III were 57.7, 77.4, and 91.2%, with specificities of 88.9, 85.3, and 91.4%, respectively [63]. Therefore, the detection of AF infection by PCR and inflammation using cytokine levels is considered to be important for assessing the status of PTL.

4.6 Clinical Benefits of Antibiotics for Subclinical Intrauterine Infection in Cases of PTL

A Cochrane review reported that the current usage of antibiotics is associated with adverse effects in neonates, such as cerebral palsy, but is also beneficial for mothers [64]. Preterm birth may be caused not only by intrauterine infection, but also by sterile intrauterine inflammation. Therefore, antibiotic therapy may not prevent preterm birth with sterile intrauterine inflammation. Combs et al. reported that antibiotics may be useful in cases of PTL without severe intra-amniotic inflammation that test positive for microorganisms [65]. Therefore, the selection of patients is important for decision-making regarding antibiotic therapy.

Our highly sensitive and reliable PCR system revealed that antibiotic therapy increased the risk of preterm birth in cases of PTL without intra-amniotic microorganisms, but may prolong the gestation period in cases of PTL with microorganisms. In brief, antibiotic therapy may have detrimental effects in cases of PTL without microorganisms, but may be beneficial for those with microorganisms in the amniotic cavity [66]. As a possible explanation, antibiotic therapy is only effective in intra-amniotic infection cases. In sterile intra-amniotic inflammation cases, antibiotic therapy has adverse effects on PTL. We previously reported that the number of intestinal *Clostridium* species was very low in preterm delivery cases [67]. Intestinal *Clostridium* has been shown to play an important role in the induction of regulatory T (Treg) cells, which contribute to the regulation of inflammation. Therefore, antibiotic therapy may decrease the number of *Clostridium* species that induce Treg cells. Decreased Treg cell numbers did not regulate inflammation, and resulted in preterm delivery. Therefore, antibiotic therapy needs to be selected for intra-amniotic infection cases only.

4.7 Conclusions and Future Directions

The accurate detection of microorganisms in AF by highly sensitive and reliable PCR is essential for the management of PTL. The degree of intrauterine inflammation may be evaluated by the quantification of AF cytokines such as IL-8, IL-6, and MCP-1. The management of PTL based on the presence of microorganisms and inflammation in AF will improve the outcomes of future PTL cases.

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Clinical and Subclinical Intrauterine Infection or Inflammation

5

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Abstract

Intrauterine infection and inflammation are the major causes of preterm labor and/or preterm prelabor rupture of membranes (pPROM). Numerous cytokines and chemokines, matrix metalloproteases, and toll-like receptors are involved in the mechanisms of preterm labor and pPROM. Ascending infection from the vagina and cervix is thought to be the most common pathway of intrauterine infection. The prevalence of positive amniotic cultures is 9–38% in preterm labor with intact membranes and 12–34% in pPROM. Analysis by PCR results in a higher prevalence of 11–56% in preterm labor with intact membranes and 18–50% in pPROM. The optimal diagnostic criteria are not well established. Histological examination of the placenta, fetal membranes, and umbilical cord or amniotic fluid analysis is the gold standard for the diagnosis of intrauterine infection. Multiple organ systems, including the hematopoietic system, thymus, adrenal glands, skin, kidneys, heart, lungs, and brain, are targeted in fetal inflammatory response syndrome. However, there is a lack of robust meta-analysis-based evidence regarding the association between intrauterine infection/inflammation and adverse neonatal outcomes in preterm infants because of various confounding factors.

Keywords

Chorioamnionitis · Preterm birth · Prelabor premature rupture of membranes Cerebral palsy · Bronchopulmonary dysplasia

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5.1 Introduction

Intrauterine infection and inflammation are the major causes of preterm labor and/or preterm prelabor rupture of membranes (pPROM). Benirschke, a pathologist, proposed the idea that intrauterine infection is related to preterm birth and neonatal sepsis by showing representative cases and clinical data of histological chorioamnionitis for the first time in 1960 [1]. Following this, Bobitt et al. reported studies, in 1977 and 1978, showing direct evidence that positive amniotic fluid culture of samples from a transcervical needle or intrauterine catheter was associated with preterm delivery and neonatal sepsis [2, 3]. The issue with these studies is that amniotic fluid could be contaminated because of transcervical sampling. In 1979, Garite et al. reported the utility of transabdominal amniocentesis for the diagnosis of intraamniotic infection in pPROM [4]. Histological findings of chorioamnionitis and amniotic fluid analysis obtained by transabdominal amniocentesis are widely studied to assess the association between intrauterine infection and preterm birth. Several studies have confirmed that intrauterine infection causes preterm delivery. Furthermore, the concept of fetal inflammatory response syndrome (FIRS), the condition of inflammation spread to the fetus, is a research focus from the point of view of neonatal prognosis.

5.2 Definitions

Since various terminologies are used to express intrauterine infection/inflammation in this field, confusion frequently occurs. In this chapter, we use terminology according to the original reference; the standard definitions of each term are described here.

5.2.1 Intrauterine Infection

Intrauterine infection is the condition of infection in one or more of the intrauterine components, including the decidua, chorion, amnion, placenta, umbilical cord, fetus, and amniotic fluid. Therefore, this term is usually used in a broad sense.

5.2.2 Chorioamnionitis

Chorioamnionitis is most frequently used as a representative term for intrauterine infection in both clinical practice and research. We should note that this term usually implies heterogeneous conditions; however, strictly speaking, chorioamnionitis is the condition of inflammation in the chorion (and amnion).

Chorioamnionitis is often divided into clinical chorioamnionitis and histological chorioamnionitis or clinical chorioamnionitis and subclinical chorioamnionitis. Clinical chorioamnionitis defines pregnant women with obvious intrauterine

infection diagnosed by clinical findings. Histological chorioamnionitis is diagnosed by histological analysis of the placenta and fetal membranes. Histological chorioamnionitis is sometimes recognized as the same condition as subclinical chorioamnionitis.

5.2.3 Intraamniotic Infection

Intraamniotic infection is defined as the presence of a microorganism(s) in the amniotic fluid, usually accompanied by inflammation. When accompanied by intrauterine infection diagnosed by clinical findings, this condition has also been referred to as intraamniotic infection in some studies.

5.2.4 Intraamniotic Inflammation

Intraamniotic inflammation is defined as the presence of positive makers of inflammation in the amniotic fluid. The marker varies in each study.

5.2.5 Microbial Invasion of the Amniotic Cavity (MIAC)

MIAC is defined as the presence of microorganism(s) in the amniotic fluid, regardless of the presence or absence of inflammation.

5.2.6 Intrauterine Inflammation or Infection or Both (Triple I)

This term was proposed by the NICHD expert panel to clarify that inflammation can occur without infection and to avoid using histological inconsistency of "chorioamnionitis" [5]. Suspected triple I is defined as the presence of fever (≥39 °C or ≥38 °C for 30 min) accompanied by either fetal tachycardia (>160 bpm for 10 min or longer), maternal leukocytosis (WBC > 15,000/mm^3), or purulent fluid from the cervical os. Triple I is confirmed by histological findings of the placenta and umbilical cord or by amniotic fluid findings.

5.3 Biochemical Mediators Associated with Preterm Delivery Caused by Intrauterine Infection/Inflammation

5.3.1 Pro-Inflammatory Cytokines and Chemokine

Microorganism invasion to the intrauterine cavity stimulates decidua and fetal membranes to produce cytokines and chemokines resulting in an increase of prostaglandin synthesis [6]. In human studies, pro-inflammatory cytokines and

chemokines, such as IL-1β, TNF-α, IL-6, and IL-8, have been found to be increased in the amniotic fluid in cases of preterm labor or pPROM with intraamniotic infection [7–11]. The presence of IL-6 in the amniotic fluid is widely used as a marker of intraamniotic infection/inflammation [9, 10]. Sadowsky et al. have reported the role of cytokines in preterm labor by infusion of cytokines into amniotic fluid in nonhuman primates. Infusion of IL-1β resulted in the most intense uterine contraction resulting in preterm delivery in all five animals. TNF-α infusion also resulted in moderate intensity uterine contraction in three of the five animals and preterm delivery in two of the five animals. Infusion of IL-1β or TNF-α into amniotic fluid was associated with increased levels of various biochemical mediators including IL-1β, TNF-α, IL-6, IL-8, prostaglandins, MMP-9, and leukocytes. On the other hand, neither IL-6 nor IL-8 infusion induced an increase in uterine contractions or preterm delivery. Neither IL-6 nor IL-8 was associated with increased levels of IL-1β or TNF-α [12]. In a mouse study, IL-1 infusion induced preterm labor, which was prevented by pretreatment with an IL-1 receptor antagonist [13]. A TNF-α antagonist also prevented preterm delivery induced by lipopolysaccharide (LPS) [14]. These studies suggest that IL-1β and TNF-α play an important role in the initiation of preterm delivery rather than IL-6 or IL-8.

5.3.2 Anti-Inflammatory Cytokines

Levels of anti-inflammatory cytokines, such as IL-10, IL-4, and IL-13, in amniotic fluid are decreased in patients with intraamniotic infections at term [15]. In a pPROM study, IL-10 in the amniotic fluid was found to have a high sensitivity and specificity for the prediction of funisitis [16]. The administration of IL-10 prevents preterm delivery induced by LPS in a rat study [17].

5.3.3 Matrix Metalloproteases (MMPs)

MMPs are family of zinc enzymes and the major proteases in extracellular matrix protein degradation. MMPs play an important role in rupture of membranes at term, preterm, and during parturition. In pregnant women with pPROM, high levels of MMP-1, MMP-8, and MMP-9 in the amniotic fluid are associated with the condition [18–21]. MMP-3, MMP-7, and MMP-8 levels in the amniotic fluid are increased in pregnant women with preterm delivery [19, 22, 23]. Moreover, MMP-1, MMP3, MMP7, MMP-8, and MMP-9 levels are increased in pregnant women with preterm intraamniotic infection, regardless of the membrane status [18–23]. These findings suggest that MMPs degrade fetal membranes leading to pPROM and promote remodeling of the collagen in the cervix leading to cervical ripening that results in preterm birth.

5.3.4 Toll-Like Receptors (TLRs)

TLRs are a family of pattern-recognition receptors that recognize conserved molecular products derived from microorganisms. Recognition of TLR ligands results in an acute innate response and mediates the adaptive immune system [24]. Soluble TLR-1, TLR-2, TLR-4, and TLR-6 levels in the amniotic fluid are increased in pPROM with MIAC [25, 26]. TLR-4 recognizes LPS from gram-negative bacteria and cell wall mannan from Candida species. TLR-2 recognizes peptidoglycan from gram-negative bacteria and phospholipomannan from Candia species. TLR-1/2 or TLR-6/2 recognizes diacyl or triacyl lipopeptides from bacteria and mycoplasma [26]. In a nonhuman primate study, a TLR-4 antagonist inhibited the production of cytokines and prostaglandins, and prevented preterm uterine contractions induced by LPS [27].

5.4 Routes of Infection

1. Ascending infection from the vagina and the cervix

   Ascending infection from the vagina and cervix is thought to be the most common pathway of intrauterine infection. Several findings support this concept. Histological chorioamnionitis is more common and severe at the site of the membrane rupture. The microorganisms identified from the amniotic fluid are similar to those in the vagina and enteric flora. In a twin pregnancy, histologic chorioamnionitis is more common in the first twin than in the second twin [28]. Culture results of amniotic fluid were also found to be more positive for the first twin sac [29]. The timing of ascending into the uterine cavity is not well understood, but it most likely varies among individual pregnant women.

   A staging classification was proposed to understand the process of microorganism invasion into the uterus and fetus [28].

   Stage I. Microorganisms overgrow in the vagina and cervix. Bacterial vaginosis is a representative condition, described in Chap. 18.

   Stage II. Microorganisms reach the decidua and chorion via the cervical canal. A local inflammatory response leads to deciduitis and chorioamnionitis.

   Stage III. Microorganisms invade the amniotic fluids (intraamniotic infection). The fetal vessels are also involved in this stage (funisitis).

   Stage IV. The fetus aspirates or swallows microorganisms or the umbilical cord is directly infected, resulting in fetal infection.
2. Transplacental/hematogenous infection

   The microorganisms in maternal circulation invade the intervillous space and spread to the villi and fetus. Once the placenta is infected, the placenta itself can become an infection nidus. Recent studies suggest that oral microbiota can hematogenously transfer to the placenta [30, 31].

3. Retrograde infection from the peritoneal cavity via fallopian tubes
   This rarely occurs as intraperitoneal infection during pregnancy is not frequent and the fallopian tubes are functionally obstructed.
4. Transabdominal infection (Iatrogenic infection)
   Invasive procedures such as amniocentesis, percutaneous umbilical blood sampling, fetoscopic laser surgery, and fetal shunt surgery can allow direct inoculation of the maternal skin flora into the uterine cavity. Maternal complications including chorioamnionitis related to transabdominal amniocentesis are rare and are estimated to occur in <1/1000 [32].

5.5 Microbiology

Intrauterine infection is usually polymicrobial in 24–67% of cases [33] and involves both aerobic and anaerobic bacteria.

The prevalence of microbial invasion of the amniotic cavity is different between culture-based methods and PCR-based methods, preterm labor, and pPROM. A review published in 1988 reported the prevalence of positive amniotic culture as 16% (0–48%) in preterm labor with intact membranes, and 28% (15–43%) in pPROM [28]. A recent review in 2012 has reported the prevalence of positive amniotic culture as 9–38% in preterm labor with intact membranes, 12–34% in pPROM. Analysis by PCR results in a higher prevalence of 11–56% in preterm labor with intact membranes and 18–50% in pPROM [33]. However, identification of microorganisms in the amniotic fluid by PCR is not commonly performed in clinical practice. The utility of PCR in clinical practice is not well established. We need to be cautious in our interpretation of PCR results, which can detect non-viable microorganisms and has a high incidence of false positives caused by contamination.

Ureaplasma species and *Mycoplasma hominis* are the most frequent microorganisms, although the diversity of microorganisms varies among studies. Interestingly, *Ureaplasma urealyticum* colonization detected by PCR in amniotic fluid in the second trimester is associated with preterm birth [34, 35]. *Fusobacterium* species, *Bacteroides* species, Group B *streptococcus*, *Escherichia coli*, *Gardnerella vaginalis*, and *Candida* species are also frequently detected.

5.6 Intraamniotic Inflammation

Intraamniotic inflammation is not always caused by infection. Several studies have shown that “sterile” inflammation also causes preterm birth and adverse fetal/neonatal outcomes. Yoon et al. reported that intraamniotic inflammation, which was defined as a negative amniotic fluid culture but an elevated IL-6 level in the amniotic fluid, was more common than intraamniotic infection in pregnant women with preterm labor and intact membranes. Pregnant women with intraamniotic inflammation are associated with short latency and high rates of adverse neonatal morbidity, compared with those without intraamniotic infection or inflammation. The prevalence of adverse outcomes was similar between intraamniotic infection and intraamniotic

inflammation [36]. Combs et al. followed this study using PCR to avoid false negatives that occur in the culture method in preterm labor with intact membranes. The latency and the prevalence of composite perinatal morbidity and mortality were similar between the intraamniotic infection group and inflammation group [37]. Interestingly, the colonization group (PCR positive but no elevation of IL-6) and negative group (PCR negative and no inflammation) had similar outcomes.

The mechanisms of intraamniotic inflammation are still not fully understood, and viral infection may be one of the causes. Recent studies have shown that damage-associated molecular patterns (DAMPs) can be involved in intraamniotic inflammation. High-mobility group box 1 (HMGB1), which is one of the DMAPs, is a ubiquitous nuclear protein secreted by cells of innate immunity in response to pathogenic products and by injured or dying cells. HMGB1 plays an important role in the intersection of the host inflammatory response to sterile and infectious insults [38]. HMGB1 levels are increased in amniotic fluid during intraamniotic infection/inflammation. Immunoreactive HMGB1 is localized in amnion epithelial cells, stromal cells in Wharton's jelly, myofibroblasts and macrophages in the chorioamniotic connective tissue, and infiltrating neutrophils. The authors propose that HMGB1 is released from injured cells into amniotic fluid, leading to intraamniotic inflammation without microbial invasion [39]. Further studies are required to fully understand the mechanisms of intraamniotic inflammation.

5.7 Clinical Signs and Laboratory Tests

Fever, maternal tachycardia, fetal tachycardia, maternal white blood cell count, uterine tenderness, and purulent discharge are commonly used for diagnosis of intrauterine infection. Careful assessment requires these clinical findings are modified by labor pain, epidural anesthesia, antenatal corticosteroid, β stimulant, and acetaminophen. In addition, neither of them is specific to intrauterine infection. Ruling out infection/inflammation in other organs is also important.

5.7.1 Fever

A cut-off value of 37.8 °C or 38.0 °C is commonly used in studies. Fever of ≥39 °C or 38–38.9 °C on two occasions 30 min apart is adopted for suspected triple I [5]. In a term study, fever (≥38 °C) had a sensitivity of 42% and a specificity of 86.5% for the prediction of histological chorioamnionitis. Fever also had an odds ratio of 2.54 (95% confidence intervals 1.59–4.06) for the prediction of fetal inflammatory response [40].

5.7.2 Maternal Tachycardia (>120 bpm)

The diagnostic performance of fever in preterm labor or PROM is not well studied. In a term study, maternal tachycardia had a sensitivity of 47% and a specificity of 70% for the prediction of histological chorioamnionitis [40].

Fetal Tachycardia (>160 bpm)
In a pPROM study including gestational age between 26 and 35, fetal tachycardia had a sensitivity of 8% and a specificity of 97% for the prediction of histological chorioamnionitis [41].

Uterine Tenderness
This clinical finding may be more specific than other clinical signs. However, this finding is less objective, and its diagnostic performance is unclear.

Purulent Fluids from the Cervical Os
Purulent fluids including discharge in intact membranes or amniotic fluid in pPROM are also more specific, but less objective. Cervicitis can be causative for purulent discharge.

Maternal White Blood Cell Count
The optimal cut-off value has not been established, but 15,000/mm^3 is commonly used. When a cut-off value of 11,800/mm^3 was used, sensitivity was 63% and specificity was 61% for the prediction of histological chorioamnionitis in pregnant women with preterm delivery [42]. Antenatal glucocorticoid leads elevation of white blood cell count.

C-Reactive Protein
The optimal cut-off value has not been established. Various cut-off values were reported, ranging from 0.5 to 4.0 mg/dL [43]. Sensitivity and specificity vary among studies. In pregnant women with premature rupture of membranes at >28 weeks of gestation, sensitivity was 56% and specificity was 58% for the prediction of histological chorioamnionitis when a cut-off value of 0.5 mg/dL was used [44]. On the other hand, a sensitivity of 88% and a specificity of 96% for the prediction of histological chorioamnionitis at a cut-off value of 1.25 mg/dL were reported in pregnant women with pPROM at <34 weeks of gestation [45]. A systematic review concluded that there was no clear evidence to support that fact that CRP was useful for the early diagnosis of chorioamnionitis in pPROM [43].

Procalcitonin
At a cut-off value of 0.054 ng/mL, the sensitivity and specificity were 92% and 68%, respectively, in pregnant women with pPROM for the prediction of histological chorioamnionitis [46].

5.8 Diagnosis

5.8.1 Clinical Criteria

The optimal diagnostic criteria are not well established. The criterion used in the study by Gibbs [47], that is, the presence of fever (≥37.8 °C) accompanied by more than two of the following clinical signs: maternal tachycardia (>100 bpm), fetal

tachycardia (>100 bpm), leukocytosis (white blood cell count (WBC ≫ 15,000/mm^3)), uterine tenderness, and foul-smelling amniotic fluid, is commonly used in research. Note that in the study by Gibbs participants were pregnant women with rupture of membranes at term; thus, whether this criterion is useful in pregnant women with preterm labor or pPROM is unclear.

As mentioned above, the new concept of triple I was proposed in 2015. Triple I is diagnosed on the basis of the presence of fever (≥39 °C or ≥38 °C for 30 min) accompanied by either fetal tachycardia (>160 bpm for 10 min or longer), maternal leukocytosis (WBC > 15,000/mm^3), or purulent fluid from the cervical os. However, the utility of this criterion has not yet been studied.

Histological examination of the placenta, the fetal membranes, and the umbilical cord, or amniotic fluid analysis is the gold standard for the diagnosis of intrauterine infection.

5.8.2 Histological Examination of the Placenta, the Fetal Membranes, and the Umbilical Cord

The presence of acute inflammatory lesions with the infiltration of neutrophils in the placenta, fetal membranes, and umbilical cord by pathohistological examination is the most frequent diagnostic method. We need to be cautious, however, as these findings can occur due to not only infection but also sterile inflammation. When inflammatory lesions are found in in the decidua, chorion, amnion, villi, and umbilical cord, they are referred to as deciduitis, chorioamnionitis (or amnionitis), villitis, and funisitis, respectively.

Grading and staging classifications vary among clinical practices and research. The classification recommended by the Amniotic Fluid Infection Nosology Committee of Perinatal Section and the Society for Pediatric Pathology and reported by Redline et al. in 2003 has recently gained popularity [48]. Neutrophils in inflammatory lesions in the chorion and amnion migrate from the maternal vessels in the decidua [49], whereas those in the umbilical cord are of fetal origin. Therefore, the location of neutrophil infiltration in the lesions is useful in distinguishing between a maternal inflammatory response and fetal inflammatory response [50].

The earlier the gestational age at delivery, the higher the incidence of chorioamnionitis, indicating an important role in early preterm birth [51]. There is also a stepwise increase in neonatal morbidities and mortality according to histological stage and grade of maternal inflammatory response and fetal inflammatory response [52]. Another group has also reported that increasing stage or grade of maternal and fetal inflammation is associated with an earlier gestational age resulting in incremental incidence of neonatal morbidity [53].

Funisitis, inflammatory lesions in the umbilical cord, is representative of a fetal inflammatory response. There is an association between funisitis and a high fetal plasma IL-6 level [54]. Moreover, the higher the stage of funisitis is, the higher the IL-6 levels in the amniotic fluid are [55]. Therefore, funisitis is the histological counterpart of the fetal inflammatory response.

The clinical limitation of histological findings of inflammation in the placenta and umbilical cord is that these findings are available only after delivery.

5.8.3 Amniotic Fluid Analysis

Amniotic fluid analysis results in direct evidence of intraamniotic infection (and inflammation).

Early studies have reported that intraamniotic infection was detected in pregnant women with preterm labor or pPROM and no signs of infection. Furthermore, the first key review of intraamniotic infection and preterm labor in 1988 reported that among pregnant women with a positive amniotic fluid culture, the prevalence of clinical chorioamnionitis was only 58% in those with preterm labor and intact membranes and only 46% in those with pPROM [27]. These findings suggest that preterm labor and pPROM themselves are manifestations of intraamniotic infection/inflammation. Moreover, a recent study has shown that 24% of pregnant women with clinical chorioamnionitis in preterm have no intraamniotic infection or inflammation [56].

Although the reliability of clinical criteria for detection of IAI in women with preterm labor or pPROM is not high enough, routine transabdominal amniocentesis in pregnant women with preterm labor or pPROM to detect intraamniotic infection/inflammation is not popular [57, 58]. This is because transabdominal amniocentesis itself is associated with a risk of infection and rupture of membranes, although uncommon. In addition, there is no robust evidence to support the fact that management with transabdominal amniocentesis improves neonatal outcome in preterm labor or pPROM. Only a small retrospective study has shown that routine transabdominal amniocentesis is useful for improvement of neonatal outcome in neonates born at 22–28 weeks of gestation [59]. Nevertheless, direct sampling of the amniotic fluid can provide variable information for decision-making on clinical management. Clinicians should consider transabdominal amniocentesis when intraamniotic infection/inflammation cannot be ruled out.

5.8.4 Culture

Culture for aerobic, anaerobic, and genital mycoplasmas should be included. However, culturing for mycoplasmas missed 40% of cases, compared with PCR [60].

5.8.5 Gram Stain

Sensitivity is 63% and specificity is 99% in patients with preterm labor and intact membranes [9]. Sensitivity is 24% and specificity is 99% in patients with pPROM [10].

Genital mycoplasmas cannot be detected by Gram staining as they lack a cell wall. Other markers should be referred to when intraamniotic infection/inflammation is suspected.

5.8.6 Glucose

When the cut-off value of ≤14 mg/dL is adopted, the sensitivity is 82% and specificity is 82% in patients with preterm labor and intact membranes [9]. The sensitivity is 71% and specificity is 52% in patients with pPROM [10].

5.8.7 WBC Count

When a cut-off value of >50 mg/dL is adopted, the sensitivity is 64% and specificity is 95% in patients with preterm labor and intact membranes [9]. The sensitivity is 53% and specificity is 84% in patients with pPROM [10]. Elevated leukocyte levels on Gram staining (>2 per high-power field on microscopy) are also useful [59].

Both glucose levels and WBC count are useful for the detection of intraamniotic infection.

5.8.8 IL-6

Although IL-6 is the most reliable and popular marker for intraamniotic infection/inflammation, its detection is not practical in clinical practice as it takes time to obtain results. A rapid bed-side test is available in some countries [61].

When the cut-off value of ≥11.3 ng/mL is adopted, the sensitivity is 100% and specificity is 83% in patients with preterm labor and intact membranes [9]. The sensitivity is 81% and specificity is 75% in patients with pPROM [10].

5.8.9 MMP-8

Studies using MMP-8 have recently been increasing. A rapid bed-side test is also used in research [62]. MMP-8 has a higher specificity for the detection of intraamniotic infection than does IL-6 [63].

5.8.10 Leukocyte Esterase Activity

Leukocyte esterase activity using a urine dipstick reagent strip (Chemstrip 9) has a sensitivity of 91% and a specificity of 95% for the diagnosis of clinical chorioamnionitis [64].

5.8.11 Lactate Dehydrogenase (LDH)

Increased LDH (>429 IU/L) has sensitivity of 87% and specificity of 38%. The combination of increased LDH and decreased glucose (<0.7 mmol/L ≒ 13 mg/dL) has sensitivity of 67% and specificity of 66% [65].

5.9 Treatment

Prompt initiation of antibiotic therapy and delivery are the principle treatments for intrauterine infection [66]. However, expectant management is often attempted due to prematurity. The optimal timing of labor induction has not been established. It depends on gestational age, the severity of infection/inflammation, fetal well-being, and institutional ability.

There is no evidence of harm induced by antenatal corticosteroids in intrauterine infection, although their use is controversial. Theoretically, corticosteroids can exacerbate infection. Several studies have indicated the benefit of using antenatal corticosteroids in intrauterine infections. A meta-analysis has concluded that antenatal corticosteroids are safe and can reduce neonatal complications in preterm birth associated with chorioamnionitis [67].

Antibiotic treatment is discussed in Chap. 13.

5.10 Prognosis

5.10.1 Maternal Complications

Intrauterine infection is associated with abnormal uterine function leading to dystocia and uterine atony that results in increased risks of cesarean section and postpartum hemorrhage [68, 69]. The longer duration of infection is a risk factor for uterine atony at term [70].

The incidence rates of endomyometritis, wound infection, pelvic abscess, and bacteremia are also increased two–fourfold [58]. The prevalence of bacteremia is approximately 10% in pregnant women with intrauterine infection, and it commonly involves group B *streptococcus* and *E. coli* [66].

5.10.2 Neonatal Complications

Intrauterine infection/inflammation is the leading cause of preterm birth. Furthermore, once an infection/inflammation reaches the fetus, the fetal immune system activates and injures fetal organs. In 1998, Gomez et al. reported high IL-6 levels in fetal plasma in preterm labor or pPROM were associated with a higher prevalence of severe neonatal morbidity and proposed a concept of fetal inflammatory response syndrome (FIRS) [71]. A key review in 2007 demonstrated that multiple organ systems, including the hematopoietic system, thymus, adrenal

glands, skin, kidneys, heart, lungs, and brain, are targeted in FIRS [72]. Since then, numerous studies have attempted to establish that infection/inflammation in a fetus contributes to adverse neonatal outcomes. However, there is a lack of robust evidence of the association between intrauterine infection/inflammation and adverse neonatal outcome in meta-analysis in preterm infants. This may be because of various confounding factors such as gestational age, different inclusion criteria, various classification criteria, no information of duration, intensity, or microorganisms involved. Especially, most studies were assessed from the standpoint of "chorioamnionitis," although chorioamnionitis is a maternal inflammatory response. We need to put a weight on the concept of the fetal inflammatory response (funisitis or fetal plasma cytokines, if available) rather than the maternal inflammatory response.

5.10.3 Brain Injury

Pro-inflammatory cytokines activate vasoactive inflammatory mediators, leading to a change in blood–brain barrier permeability, coagulation and thrombosis, and endothelial damage. Direct microbial invasion can occur in this condition. Moreover, preoligodendrocytes in white matter are injured by direct injury or activation of microglia by pro-inflammatory cytokines, leading to abnormal myelin formation and periventricular leukomalacia (PVL) or cerebral palsy [73].

There is a discrepancy of the result for the effect of chorioamnionitis on neurodevelopmental outcome in preterm in human. The first meta-analysis on the association between chorioamnionitis and neurodevelopmental outcome was published in 2000 and reviewed 26 studies. Clinical chorioamnionitis was significantly associated with CP (relative risk (RR), 1.9; 95% confidence intervals (CI), 1.4–25.) and cystic PVL (RR, 3.0; 95% CI, 2.2–4.0) in preterm infants. Histological chorioamnionitis was also associated with cPVL (RR, 2.1; 95% CI, 1.3–16.2) [74]. The second meta-analysis, including studies published between 2000 and 2009, was reported in 2010. Fifteen studies were reviewed. Clinical chorioamnionitis had a pooled odds ratio of 2.42 (95% CI, 1.52–3.84) and histological chorioamnionitis had a pooled odds ratio of 1.83 (95% CI, 1.52–3.84) for CP [75]. This meta-analysis included both term and preterm infants. A meta-analysis including 84 studies, published in 2012, has shown chorioamnionitis is not a risk factor for adverse neurodevelopment in preterm infants. Interestingly, they concluded that inflammation can enhance brain maturation in preterm infants [76]. The most recent meta-analysis published in 2017 has shown that the prevalence of CP was significantly increased in preterm infants with histological chorioamnionitis (risk ratio 1.34) but not in those with clinical chorioamnionitis [77]. In a study by Ylijoki et al., it was reported that antenatal corticosteroids reduce the adverse effects of inflammation on the developing nervous system [76]. There are few studies that focused on the association between funisitis (fetal inflammatory response) and CP or PVL. Salas et al. reported that the prevalence of severe neurodevelopmental impairment and death was higher in infants with subacute necrotizing funisitis compared with infants without placental/umbilical cord inflammation [78].

A meta-analysis on the association between chorioamnionitis and intraventricular hemorrhage (IVH) in preterm infants was also reported. Chorioamnionitis was significantly associated with all grade IVH (odds ratio (OR) 1.88, 95% CI, 1.61–2.19) as well as with grade 1–2 IVH (OR 1.69, 95% CI, 1.22–2.34) and with grade 3–4 IVH (OR 1.62, 95% CI, 1.42–1.85). Meta-regression and subgroup analysis did not show an association between earlier gestational age and lower birth weight and the risk of IVH in preterm infants with chorioamnionitis. However, the presence of funisitis was not associated with an increased risk for IVH [79].

In the most recent meta-analysis, chorioamnionitis is associated with poorer mental development in preterm and very preterm infants. Clinical chorioamnionitis also affects motor development [80].

5.10.4 Lung Injury

Direct inhalation of microorganism(s), microbial products, and cytokines causes fetal lung injury in utero. In a sheep study, the administration of endotoxin into amniotic fluids leads to an increase of synthesis of surfactant proteins (SP-A, B, C, and D) within 12–24 h to 2 weeks, suggesting endotoxin exposure enhances the lung maturation. However, endotoxin infusion inhibits vascular development and endothelial nitric oxide synthase decreases in the small vessels within 2 days in the fetal lung. Smooth muscle hypertrophy in the distal pulmonary arterioles also occurred by day 7, suggesting endotoxin exposure causes the anatomic changes of bronchopulmonary dysplasia (BPD) [81]. Intraamniotic infection/inflammation can mature and injure the fetal lung.

In human studies, there is a discrepancy in the respiratory outcome results across studies [82]. In a meta-analysis study including 59 studies, the pooled adjusted OR was 1.58 (95% CI, 1.11–2.24). However, the authors emphasized that there was strong evidence of publication bias, which suggests potential overestimation of association between chorioamnionitis and BPD [83].

5.10.5 Patent Ductus Arteriosus (PDA)

The effect of intrauterine infection/inflammation on PDA is also controversial. Park et al. reviewed a total of 23 studies. Chorioamnionitis was associated with PDA (OR 1.43, 95% CI, 1.19–1.72) [84]. On the contrary, Behbodi et al. reported the opposite result. When confounders including gestational age and body weight were taken into account, chorioamnionitis was not a risk factor for PDA [85].

In the first review, antenatal corticosteroids were found to reduce the risk of PDA (OR 0.62, 95% CI, 0.42–0.9) after chorioamnionitis [84].

5.10.6 Necrotizing Enterocolitis (NEC)

There is only one meta-analysis. This study, including 33 articles, indicated an association between clinical chorioamnionitis and NEC (OR 1.24, 95% CI, 1.01–1.52),

but histological chorioamnionitis was not associated with NEC (OR 1.39, 95% CI, 0.95–2.04). Note that histological chorioamnionitis with fetal inflammation was highly associated with NEC (OR 3.29, 95% CI, 1.87–5.78) [86].

5.10.7 Retinopathy of Prematurity (ROP)

A recent systematic review and meta-analysis including 50 studies has shown that chorioamnionitis is associated with ROP, but a meta-analysis adjusted for confounders, including gestational age, failed to demonstrate an association between chorioamnionitis and ROP [87].

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Cervical Changes 1: Morphological and Biochemical Changes

6

Naohiro Kanayama

Abstract

Delivery progresses while contractions take place and the cervical canal ripens. This phenomenon can be compared to two wheels of a car. Contractions are induced by oxytocic substances, including prostaglandin (PG) F2α and oxytocin, while increased collagen degrading enzyme activity in the cervical canal promotes cervical ripening. These processes are positioned as deliberately programmed physiological inflammatory reactions in normal delivery. Intermediate modulators, including inflammatory cytokines, play the role of upstream regulators. Changes in endocrine profiles and extensive stimulation induce these intermediate modulators. In principle, the mechanism of premature delivery is the same as that of normal delivery. In premature delivery, however, the stimulation of intermediate modulators may cause infection/inflammation, such as chorioamnionitis and uteroplacental insufficiency. Recently, researchers have pointed out that decreased progesterone might induce premature delivery. Infection/inflammation, uteroplacental circulation insufficiency, and changes in hormone profiles that overwhelm the pregnancy-sustaining mechanism are factors that induce premature delivery.

Keywords

Progesterone · Inflammatory cytokines · Chemokines · Prostaglandin E_2 (PGE_2) · Extensive stimulation

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6.1 Introduction

The mechanism of delivery has been studied in a wide variety of mammals. Although these studies have contributed significantly in clarifying the mechanism of delivery in animals, many points remain unclear in understanding the mechanism of the onset of delivery in humans. To clarify the mechanism of the onset of delivery in humans, we should first recognize the differences between humans and other animals in terms of pregnancy and delivery. Figure 6.1 shows the errors in pregnancy period by animal species. The errors in pregnancy period in rodents, including mice/rats, rabbits, and sheep, are 4%, 1.5%, and 2.7%, respectively, and, their pregnancy periods generally are determined accurately, with few errors. In these animals, the decrease in progesterone, increase in estrogen, increase in cortisol and cytokine expression seem to nearly correspond to the onset of delivery. This reflects the close control of the mechanism of the onset of delivery by the endocrine profiles (Fig. 6.2).

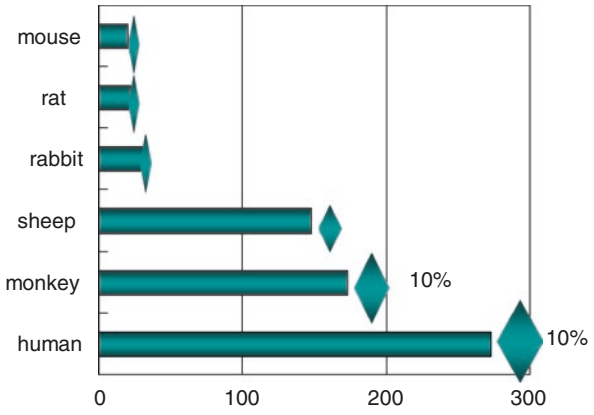

Fig. 6.1 Variation of delivery date in animals

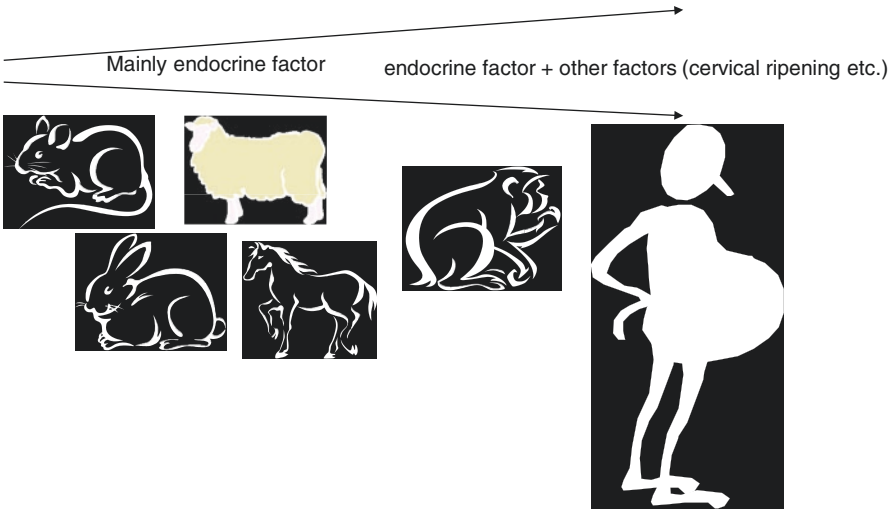

Fig. 6.2 The causes of onset of labor in human and other animals

In many animals, the endocrine profiles of mother, fetus, and placenta work in a coordinated manner to inhibit contractions in mid-pregnancy and induce the onset of contractions at the delivery stage. The hardness of the cervical canal varies from animal to animal. Compared to humans, four-footed animals have more flexible cervical canals that can be softened more easily because of a decrease in progesterone (Fig. 6.2). Therefore, it may be no exaggeration to say that uterine contractions regulate the onset and progress of delivery in four-footed animals. On the other hand, the pregnancy period ranges from 37 to 42 weeks, and the degree of variation at 5 weeks in humans. The human is regarded as an animal species that has a wide range of pregnancy periods. The difference in the cervical ripening mechanism has been pointed out as one of the reasons. Because the human is the only animal that can walk upright, compared to other animals, humans have a stronger cervical canal. Moreover, there are differences in cervical ripening from individual to individual, and the time needed for cervical ripening varies. Accordingly, in the process of human delivery, the two factors—cervical ripening and uterine contractions—should work together by playing the roles of two wheels of a car. In human delivery, cervical ripening generally precedes uterine contractions (labor pain).

How can we explain delivery from the viewpoint of biochemistry? Recently, the delivery phenomenon has been regarded as a physiological inflammatory reaction induced by various inflammatory mediators [1, 2]. Figure 6.3 shows a macroscopic finding of unripened and ripened cervix. In ripened cervix a marked edematous changes and increase of cervical mucus are observed. Samples of the neutrophil elastase, derived from the cervical canal during delivery and from the unripened cervical canal in mid-pregnancy, were stained and are displayed in Fig. 6.4. The stroma of the unripened cervix is composed of dense fibrillary elements and many fibroblasts. Neutrophil infiltration is rarely observed. The ripened cervix is characterized by the interstitial infiltration of neutrophils and swelling of the stroma. The dominant image reflects deformation of the infiltrating neutrophils and their activation. Lymphocytes and macrophages are also observed. A decrease in the fibrillary elements composing the stroma results in fluid retention, leading to swollen and edematous tissues. The histological process of tissue softening followed by

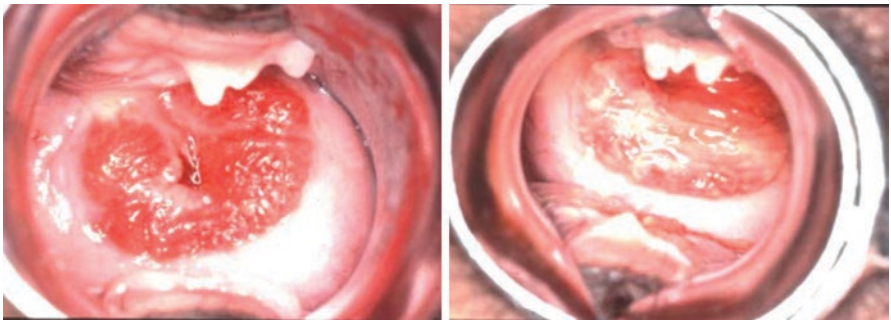

Fig. 6.3 Macroscopic findings of preterm and term cervix. Left: preterm (20w), right: term (40w)

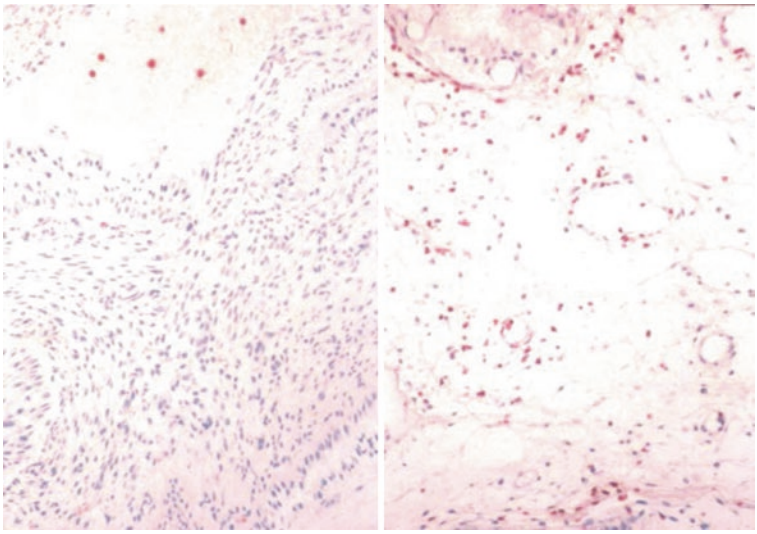

Fig. 6.4 Neutrophil elastase staining in term and preterm cervix. Right: term, left: preterm. Red color staining shows neutrophil elastase

inflammatory cell infiltration is similar to that of an inflammatory reaction. There are many related substances that are regarded as factors in inducing and regulating this physiological inflammatory reaction.

6.2 Cervical Ripening

The cervical canal is composed mainly of collagen fibers, elastic fibers, glycosaminoglycan, and cellular elements. Collagen fibers consist of type I, II, III, and IV collagen, while elastic fibers consist of elastin. Glycosaminoglycan consists of chondroitin sulfate, dermatan sulfate, and hyaluronic acid. In the cervical ripening process, degradation of the collagen and elastin fibers, increased fluid, and changes in the quality of glycosaminoglycan are regarded as the main histological and biochemical changes. Enzymes, including matrix metalloproteinase (MMP) and neutrophil elastase, degrade the matrix composed of collagen and elastin (Fig. 6.5). As the cervical canal softens, chondroitin sulfate decreases but hyaluronic acid increases. Hyaluronic acid allows the promotion of fluid retention, which leads to the softening of the cervical canal. During cervical ripening, not only hyaluronic acid but also low-molecular-weight hyaluronic acid increases in the cervical canal. Hyaluronidase and active oxygen decompose hyaluronic acid into low molecules. Low-molecular-weight hyaluronic acid induces inflammatory cytokines. These cytokines induce collagen-degrading enzymes and elastin-degrading enzymes. In this manner, the cervical canal ripens through the autocrine mechanism.

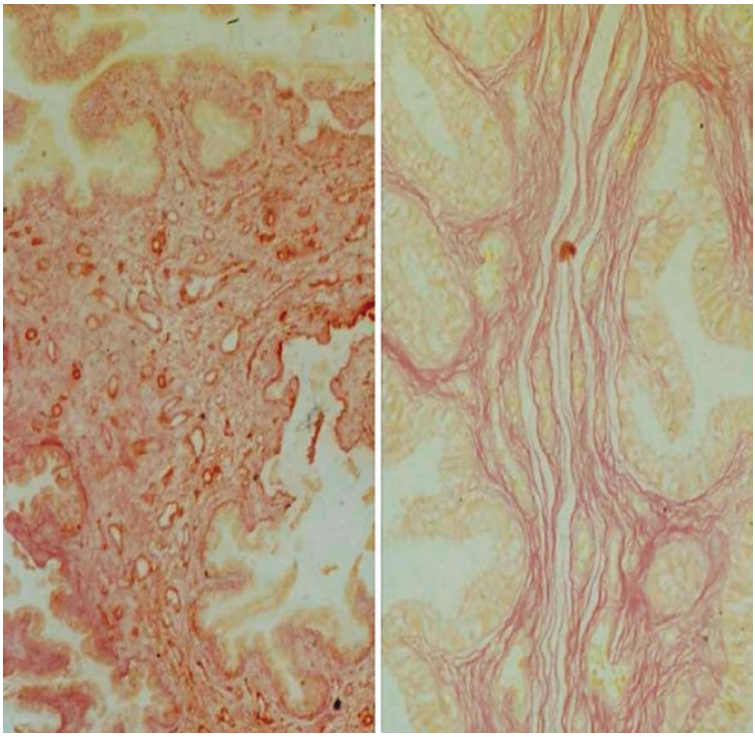

Fig. 6.5 Type I collagen staining of immature and ripened cervix. Left: immature cervix, right: ripened cervix

6.3 Contractions

Of the various uterotonic substances involved in contractions, PGE_2, $PGF_2\alpha$, and oxytocin play central roles. These uterotonic substances can be regarded as direct mediators of contractions. As PGE_2 increases in the uterus, the cervical canal ripens and the uterine muscles contract. PGE_2 and the chemokines mentioned later are important mediators that induce contractions in a coordinated manner. $PGF_2\alpha$ has the effect of promoting uterine contractions through cervical ripening. $PGF_2\alpha$ and oxytocin are the main substances in inducing strong contractions. PGE_2 and $PGF_2\alpha$, produced mainly in the egg membrane, are transferred to the decidua in the amnion fluid and induce uterine contractions. Oxytocin is a peptide containing nine amino acids that are produced in the supraoptic nucleus of the hypothalamus and the nucleus paraventricularis. Oxytocin is reported to be produced in the pregnant uterus during delivery. Oxytocin increases the intracellular Ca level via oxytocin receptors in the uterine muscles and induces strong uterine contractions. Generally, oxytocin rapidly increases in the latter half of pregnancy, and thus oxytocin seems to amplify the uterine contraction channel induced by PGs. From a clinical

viewpoint, effective contractions cannot be induced even if oxytocin is administered to a pregnant female without cervical ripening. Therefore, the above mechanism can be reasonably assumed. Oxytocin receptors express moderately in the villus, fetal membrane, decidua, and uterien muscles during pregnancy. On the other hand they express intensively in the decidua and uterine muscles during parturition. Oxytocin receptors are induced by inflammatory cytokines. This is probably why oxytocin acts minimally during pregnancy but actively during delivery.

6.4 Intermediate Modulators

Collagen-degrading enzymes and the final mediators of delivery, such as PGs, are regulated by the intermediate modulators. These intermediate modulators are produced mainly in the egg membrane and decidua. PGE2 and chemokines, produced in the egg membrane and particularly the amniotic membrane, are involved in both the onset of contractions and cervical ripening and are key mediators in the phenomenon of delivery.

6.4.1 PGE2

As a result of a decrease in progesterone in the egg membrane, production of PGE_2 and platelet activating factor (PAF) is promoted. According to a recent report, as delivery approaches the constructive protein in the egg membrane cells such as periphylline and adipophilin decrease, free fatty acids increase in the cytoplasm, and PG synthesis is promoted [3]. PGE_2 produced in the egg membrane is transferred to the amniotic fluid and uterine muscles and triggers contractions. Moreover, PGE_2 has the effect of ripening the cervical canal in addition to this strong effect of contracting the uterus. The presence of different mechanisms in a single substance reflects differences at the receptor level. PGE_2 receptors have four subtypes—EP1, EP2, EP3, and EP4—and each has a different effect on the uterus. Generally, EP1 and EP3 induce uterine contractions, while EP2 and EP4 induce cervical ripening [4].

6.4.2 Inflammatory Cytokines

During delivery, a wide variety of inflammatory cytokines are produced in the amniotic membrane, decidua, uterine muscles, and cervical canal, and they are essential mediators in promoting the progress of delivery. In particular, the cells are formed in the decidua, which is in contact with the uterus, and macrophages produce interleukin (IL)-1, IL-8, and tumor necrosis factor (TNF). These cytokines act on uterine stromal cells and produce uterotonic substances, including PGF2α, endothelin, and PAF. In the PG synthesis system, IL-1 produced in the decidua upregulates

cyclooxygenase-2 (COX-2) through the autocrine and paracrine mechanisms and downregulates PG dehydrogenase (PGDH) [5]. After production of IL-1, the local PG level increases remarkably. In this manner, decidual activation induces the production of cytokines, including IL-1 and TNF, and the synthesis of uterotonic substances.

Chemokines such as IL-8, which are classified as inflammatory cytokines, are produced in the decidua, endocervical cells, and amniotic cells. They act on the amniotic cells, decidual cells, uterine smooth muscle cells/fibroblasts, and neutrophils, and induce activation of the decidua, cervical ripening, and leukocyte migration. Therefore, they are regarded as essential cytokines for the onset of delivery. IL-8, which has a strong effect of ripening the cervical canal, has been regarded as a substance for promoting cervical ripening. However, study results are accumulating that IL-8 is a key substance for decidual activation.

6.4.3 Nitric Oxide (NO)

Local injection of NO into the cervical canal does not induce uterine contractions but it does cervical ripening. NO and IL-8 have similar effects, but NO is different from IL-8 because of its vasodilating effect. NO is involved in the cervical ripening mechanism in that NO induces PGE_2 and MMP and promotes cervical ripening. The clinical application of nitric oxide donors (NO donors) can be a useful tool in the process of cervical ripening [6].

6.4.4 Low-Molecular-Weight Hyaluronic Acid

Hyaluronic acid and CD44 or its receptor increase in the uterine cervix during late pregnancy. Although the significance of this phenomenon remains unknown, the recently discovered effect of hyaluronic acid to induce inflammatory cytokines has attracted researchers' attention. Via cytokines, hyaluronic acid retains fluid in the cervix and clearly serves as an intermediate modulator for the cervical ripening that enhances inflammatory reaction. Active oxygen and enzymes, including hyaluronidase, in the uterine cervix decompose hyaluronic acid into low molecules. This low-molecule-weight hyaluronic acid clearly has a strong effect in inducing chemokines [7, 8]. In an animal experiment, a low-molecular hyaluronic acid suppository induced marked cervical ripening. The inflammatory substances expressed during cervical ripening degrade hyaluronic acid into low molecules. Then, low-molecule-weight hyaluronic acid becomes a strong inflammation-enhancing factor and rapidly induces cervical ripening. Hyaluronic acid is composed of sugar chains. This physiological substance is present universally in mammals and birds. Because this highly safe substance does not directly induce contractions, its clinical application as a cervical ripening agent with fewer adverse reactions has been expected.

6.4.5 Cross Talk

There is cross talk among the intermediate modulators that operate the mechanism that promotes production in a synergistic manner [9]. Cross talk between PGE2 and chemokines is also important. Kelly et al. offered a hypothesis that the interrelation between PG and chemokines might play an essential role in decidual activation [10]. Their hypothesis has been supported by other research. According to their hypothesis, decidual activation depends on the promotion of vascular permeability in the decidua and neutrophil extravasation. As a result of a decrease in progesterone, COX-II is expressed in the decidual vessels and PGE2 is produced. In this manner, vascular permeability is promoted. As a result of a decrease in progesterone, IL-8 is produced by the decidual cells and macrophages. Neutrophils migrate to IL-8 through the vascular wall with increased permeability. Activated neutrophils migrating to the decidua release uterotonic substances, including PAF, leukotriene, and PG. At the same time, the levels of cytokines including IL-1, TNF, and IL-8 further increase through the autocrine and paracrine mechanisms. These cytokines act on the decidual vessels, and further production of IL-8 and PGE_2 is promoted through the positive feedback mechanism. In this manner, the decidua is rapidly activated.

Chemokines, including IL-8 and MCP, produced in the cervical canal and PGE_2 act on fibroblasts, increase MMP activity, and degrade collagen. Moreover, IL-8 and PGE2 promote the production of hyaluronic acid by fibroblasts to soften the cervical canal. There is cross talk between chemokines and PGE2, and they trigger both cervical ripening and contractions.

6.5 Mechanism of the Expression of Intermediate Modulators

6.5.1 Decrease in Progesterone

Clinically, it has been clear that cervical ripening and the onset of contractions are interrelated. To what extent has this interrelation been clarified from the viewpoint of biochemistry? In mid-pregnancy, progesterone is dominant over estrogen and inhibits the production of various inflammatory mediators. Therefore, delivery is not accelerated during this period. Cyclooxygenase II (COX-II) and PGDH are the well-known enzymes involved in the inhibition of contractions by progesterone. IL-1 acts on COX-II to produce PGE_2 and $PGF_2\alpha$, while progesterone downregulates COX-II in the uterus and maintains PGDH activation at a high level [10]. In female sheep and rodents during late pregnancy, corticotropin-releasing hormone (CRH), cortisol, and estrogen increase and progesterone decreases. These hormones are interrelated. Special attention should be directed to the fact that a decrease in progesterone results in the onset of inflammation. In animals, a decrease in progesterone is inversely correlated with the expression of various inflammatory mediators and their expression is promoted. In humans, however, a decrease in the blood

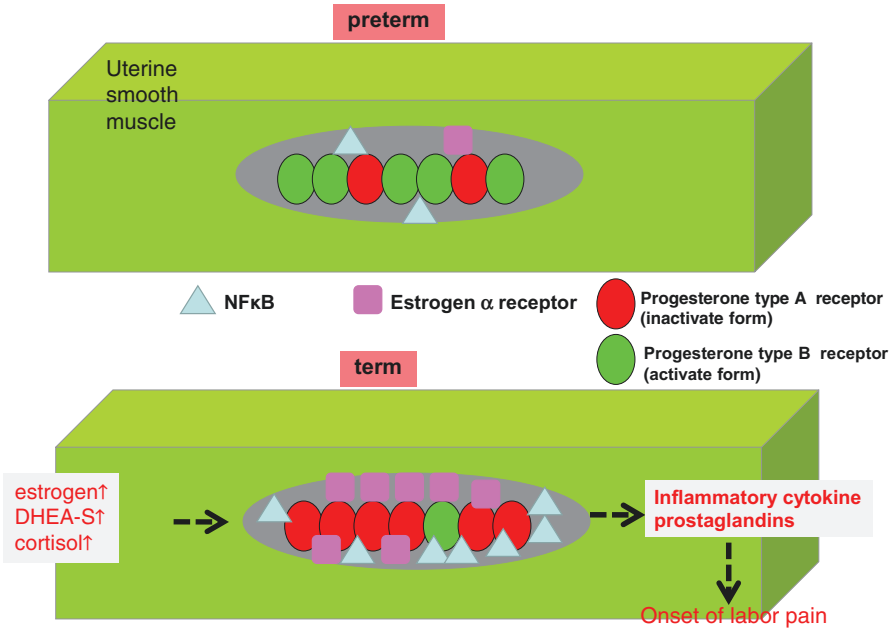

Fig. 6.6 Changes of progesterone receptor of uterine smooth muscle during pregnancy

progesterone level is not observed during late pregnancy, and the effect of progesterone has long remained unknown. According to a recent report, in humans the blood progesterone level does not change but the sensitivity of progesterone receptor A (PR-A) in the uterus and cervical canal decreases and progesterone activity declines [11]. In other words, the local activity of progesterone is adjusted according to the change in the volume ratio of progesterone receptor isoforms. Progesterone receptor B (PR-B) is an active form of PR. Compared with PR-B, PR-A is a slightly shorter molecule and binds to progesterone. However, PR-A does not transmit signals to the nucleus and competitively inhibits PR-B. In the uterine muscles after the onset of contractions, the ratio of PR-A to PR-B (PR-A/PR-B) increases and local progesterone activity declines (Fig. 6.6). As progesterone activity declines, inflammation-related substances are expressed. This mechanism has been explained by the fact that the DNA sequence of NF-κB is partially common with that of PR-B. As progesterone signals decrease, the DNA binding of PR-B also decreases. The DNA binding site of PR-B is partially common with NF-κB, an inflammation-related transcription factor. As PR-B signals decrease, NF-κB binds to the upstream region of the inflammation-related gene in the nucleus, and promotes the expression of various inflammatory substances such as chemokines, MMP, free radicals, and PGs [12].

Although RU486 was developed as an aborticide or drug to induce cervical ripening, it was not used widely in clinical settings because of its serious adverse effect of damaging the liver. RU486 is a strong drug for inducing delivery. RU486 binds to

progesterone receptors and is a progesterone antagonist. Consequently, in the uterus as progesterone activity decreases, the cervical canal ripens and contractions start. On the other hand, researchers have confirmed that such a decrease in progesterone directly induces delivery in humans. It has been demonstrated that the regular administration of progesterone to women in mid-pregnancy contributes to the prevention of premature delivery [13]. It has been speculated that progesterone may inhibit the expression of delivery-related inflammatory substances. The course of delivery can be divided into the following three stages: contraction preparation stage, contraction stage (generally delivery stage I), and delivery stage (delivery stage II). The contraction preparation stage starts once progesterone decreases.

6.5.2 CRH, Dehydroepiandrosterone Sulfate (DHEA-S)

Because corticotropin-releasing hormone (CRH) is produced in the fetus, hypothalamus of the mother, and placenta, the maternal blood CRH level increases. CRH is secreted mainly from the placenta. CRH activity is maintained at a low level during pregnancy but increases immediately before delivery [14]. CRH activity during pregnancy is regulated by CRH binding protein (CRHBP). Before delivery, CRHBP decreases, free CRH increases, and CRH activity is enhanced [15]. Accordingly, the increase in cortisol reportedly results in the downregulation of progesterone receptors. Furthermore, COX-2, a rate-controlling enzyme of PG in the placenta and amniotic membrane, is induced. COX-2 accelerates PG synthesis in the uterine muscles and the preparation for delivery is completed. CRH produced in the placenta promotes the production of cortisol and DHEA-S in the fetal adrenal gland through the umbilical cord and fetal blood circulation. DHEA-S is converted to estrogen (mainly estriol) in the placenta so that the maternal blood estrogen level can increase rapidly in the delivery preparation stage. However, exactly what estrogen induces in the delivery phenomenon remains unknown. In fact, effective contractions cannot be induced by administering estrogen to the mother. On the other hand, DHEA-S, a precursor of estrogen, is used as a drug to ripen the cervical canal in health insurance treatment. Figure 6.4 shows maternal DHEA-S levels and whether contractions were successfully promoted. If the maternal DHEA-S level is high, contractions occur smoothly [16]. The effects of DHEA-S in promoting delivery include a direct effect on the cervical canal that is not mediated by estrogen. In Japan, DHEA-S is used as a drug to ripen the cervical canal. DHEA-S is administered to mothers to prepare the endocrine profiles for delivery, and this treatment can be regarded as hormone replacement therapy for a smooth delivery.

6.5.3 Extensive Stimulation

The extensive stimulation of the uterine cervix and egg membrane by the fetus acts as an important trigger for contractions. This extensive stimulation increases the production of inflammatory cytokines and PGs in the uterine cervix and egg

membrane. In response to extensive stimulation, chemokines such as IL-8 and monocyte chemotactic protein (MCP) are produced in the egg membrane and cervical canal, and neutrophils and monocytes migrate to the lower part of uterus to produce neutrophil elastase, IL-1, and TNFα. Consequently, PGE_2, MMP, and hyaluronic acid increase in the cervix, while PGE_2 and $PGF_2\alpha$ in the uterine muscles induce contractions. During delivery, uterine contractions and cervical dilation progress in a coordinated manner. Delivery-related substances produced in response to extensive stimulation are important in this process. We often experience the following phenomena daily in clinical practice. A fetal head that does not lower prevents the onset of contractions. Detachment of the egg membrane accelerates effective contractions. Moreover, the insertion of Laminaria ensures effective cervical ripening. In the case of difficult childbirth due to insufficient cervical ripening, the progress of delivery depends largely on how effectively extensive stimulation can be given to the cervix. Ito et al. reported that the simultaneous addition of inflammatory cytokine stimulation to extensive stimulation induced a remarkable PG synthesis. This report suggests that extensive stimulation and inflammatory cytokines act in an autocrine fashion [17].

6.5.4 Amniotic Fluid

A decrease in the quantity of amniotic fluid and changes in its quality are also involved in the onset of contractions. In late pregnancy, prostanoids produced in the amniotic membrane, including PGE_2, are transferred to the amniotic fluid. Whether these prostanoids in the amniotic fluid are swallowed by the fetus and then the fetus sends a delivery signal, or the prostanoids accumulating in the amniotic fluid are transferred to the uterine muscles to affect the onset of contractions, remains unknown. Amniotic fluid is composed mainly of fetal urine. Some physiologically active substances in fetal urine regulate the mechanism for the onset of delivery. A representative substance is urinary trypsin inhibitor (UTI) or bikunin. UTI has the strong effect of inhibiting uterine contractions and a strong effect in inhibiting cervical ripening. In late pregnancy, UTI in the amniotic fluid decreases and such a substance in the amniotic fluid is also involved in the onset of contractions. UTI, which is abundant in amniotic fluid during mid-pregnancy, is reported to inhibit the expression of inflammatory cytokines in the amniotic membrane [18]. During late pregnancy, the amount of UTI in the amniotic fluid decreases, and this decrease probably promotes the production of inflammatory cytokines in the egg membrane and accelerates the onset of contractions. In an experiment using lipopolysaccharide (LPS) induced premature delivery in rat models, UTI was reported to effectively prevent premature delivery [19, 20]. A vaginal UTI suppository has been used widely for treating potential premature delivery in clinical settings. According to findings obtained from many medical institutions, a vaginal UTI suppository is remarkably effective in treating pregnant women with symptoms of potential premature delivery, such as advanced cervical ripening and prolapsed fetal membranes [21].

6.6 Mechanism of the Expression of Intermediate Modulators in Premature Delivery

In the case of a premature delivery in which cervical ripening advances abnormally early, the delivery process is similar to that of a normal delivery. Premature delivery can be regarded as a condition in which intermediate modulators, such as inflammatory cytokines, are expressed and act in mid-pregnancy when they are not expressed in normal pregnancy. In fact, in cases of premature delivery, the levels of inflammatory cytokines are reported to increase in the egg membrane, amniotic fluid, and umbilical blood [22]. Why do the inflammatory cytokines that are not induced in the normal process of pregnancy appear in the cases of premature delivery? Premature delivery can be defined as a condition in which CRH decreases in progesterone and some stimulation that is different from extensive stimulation allows intermediate modulators to act. The relevant stimulating factors are listed below.

6.6.1 Vaginitis, Cervicitis, Chorioamnionitis

Chorioamnionitis is the most common cause of natural premature delivery. When chorioamnionitis develops, LPS, a bacterium, promotes the expression of inflammatory cytokines in the uterine and egg membrane. This endotoxin triggers delivery. The most common causes of chorioamnionitis include inflammations that spread upward, such as bacterial vaginitis and cervicitis. There are a variety of causes of bacterial vaginitis and cervicitis. Foreign pathogenic microbial invasion or a stress-related, immunocompromised condition in the host may induce vaginitis and cervicitis. These causes contribute to the development of infection/inflammation in the vagina or cervical canal that spreads over the egg membrane and promotes the growth of a large amount of LPS, leading to chorioamnionitis. Many pregnant animals treated with LPS have experienced premature delivery [23]. In principle, during mid-pregnancy progesterone inhibits the expression of inflammatory cytokines. If LPS derived from chorioamnionitis overwhelms the anti-inflammatory effect of progesterone, the cascade for delivery starts and results in premature delivery.

6.6.2 Extrauterine Inflammation (Dental Caries, Periodontal Disease, etc.)

Recently, researchers have pointed out that extrauterine inflammation, such as dental caries and periodontal disease, may cause chorioamnionitis [24]. In one study that hypothesized that periodontal disease might cause premature delivery, a dental infection-study mouse was prepared by burying *Porphyromonas gingivalis* (*PG*), a periodontal pathogen, in the pulp. In this experiment, the female mouse with dental infection became pregnant and experienced premature delivery [24]. As causes of chorioamnionitis, in addition to inflammation of the vagina and cervical canal, dental caries and periodontal disease are now attracting researchers' attention. Although

details are not mentioned in this article, extrauterine inflammatory conditions, such as urinary tract infection, can also cause premature delivery [25].

6.6.3 Thrombin

In cases in which blood clots form in the placental circulation or a hematoma appears in the subchorionic hematoma, thrombin is locally produced. According to a recent report, in the presence of thrombin, blood coagulation is promoted and chemokines such as IL-8 are activated simultaneously [26, 27]. Thrombin derived from insufficient uteroplacental circulation or a subchorionic hematoma induces chemokines and activates inflammatory cytokines. From a clinical standpoint, we should understand that, in the event of bleeding from a vessel, thrombin is formed in the blood and inflammation develops immediately. The incidence of premature delivery, however, is low among pregnant women treated with aspirin over a long time [28]. We should reconfirm that bleeding and thrombus formation are risk factors in premature delivery. Bleeding is a clinical symptom that we often experience in the case of potential premature delivery. We should understand that vascular bleeding is associated with thrombin production and take appropriate action, such as frequent irrigation. Thrombi are often formed in the placental circulation of high-risk patients. Aspirin or an anticoagulant such as heparin should be administered prophylactically to these patients to prevent premature delivery. In the future, it may be important for us to control premature delivery with the relationship between inflammatory cytokines and thrombin in mind.

6.6.4 Stress

There are many reports pointing out that stress is a risk factor for premature delivery [29]. Maternal stress contributes to premature delivery in the following manner. The maternal CRH level rises, cortisol and estrogen levels increase, and the mechanism of delivery shown in Fig. 6.3 starts to activate. Moreover, stress may reduce the activity of natural killer (NK) cells in the interface between the mother and the fetus, which adversely affects the local immune mechanism and frequently induces inflammation in the interface between the two.

6.6.5 Decrease in Progesterone

The mechanism of the onset of normal delivery starts with a decrease in progesterone. A preterm decrease in progesterone may result in premature delivery [30]. This type of premature delivery is expected to occur more frequently in late preterm cases. How to make a diagnosis of premature delivery resulting from a preterm decrease in progesterone has not yet been clarified.

The summary of this chapter is shown in Fig. 6.7. Labor pain and cervical ripening are final phenomena of delivery. Intermediate modulators and final mediators of

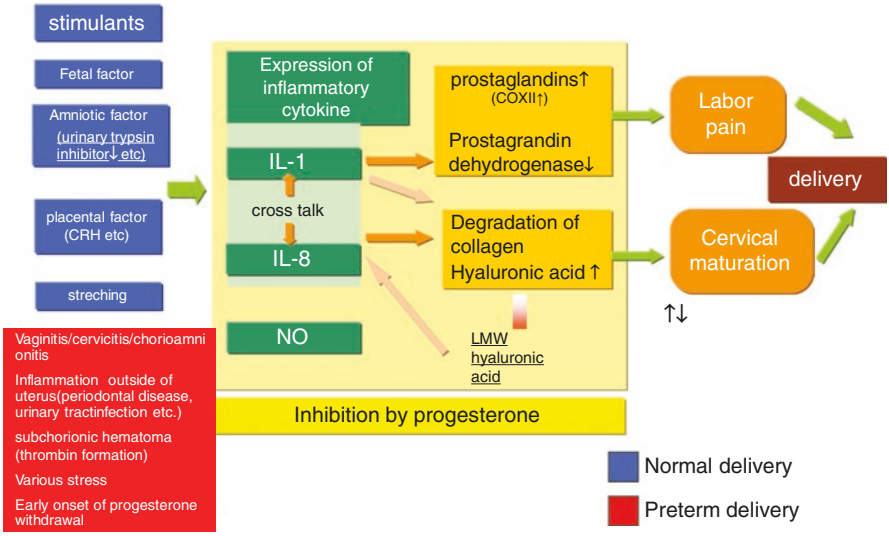

Fig. 6.7 The difference between normal delivery and preterm delivery

term delivery are nearly same as those of preterm delivery. However, their stimulants are different in preterm and term delivery. Therefore, when we consider the management of preterm delivery, it is important which stimulants are involved in the cause of preterm labor. Next to make a strategy how to remove the stimulants would be a best practice for treatment and prevention of preterm delivery.

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Cervical Changes 2: USG Findings

7

Hajime Taniguchi

Abstract

Transvaginal sonography (TVS) is widely used in clinical settings to measure cervical length. The procedure is minimally invasive, and provides objective measurements that can predict the risk of preterm delivery. There are mainly two reasons to perform TVS to measure cervical length during pregnancy. First, it can be used to identify women who are at high risk of preterm delivery during the second trimester. Second, it can be used to evaluate the progression of threatened preterm delivery over time in women who are considered at high risk of preterm delivery based on her obstetric history. As a result, TVS enables early intervention for threatened preterm delivery. However, the measurement of cervical length for threatened preterm delivery has a high negative predictive value and low positive predictive value, particularly for low-risk women. As a result, patients may be overtreated if interventions are performed simply based on the observation of short cervical length. It is therefore important to perform additional examinations to accurately identify women at risk of preterm delivery.

Keywords

Cervical length · Transvaginal sonography · Cervical incompetence

7.1 Introduction

The measurement of cervical length by transvaginal sonography (TVS) is widely used clinically to determine the risk of preterm delivery at an early stage. Compared to pelvic examination, it provides a more objective measurement [1] and is less of a

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burden to patients as it is minimally invasive and can be performed within a relatively short period of time. There are two main reasons to perform TVS to measure cervical length. First, screening of low-risk women during the second trimester can identify those who may be at risk of preterm delivery [2]. Second, imaging of high-risk women can identify those with short cervical length at an early stage, enabling early interventions. In this context, women at high risk of preterm delivery include those who have a history of preterm delivery, as well as those who have had cervical conization, multiple pregnancy, and bacterial vaginosis.

There are also several limitations with the measurement of cervical length by TVS. Specifically, the method has a high negative predictive value and a low positive predictive value. Thus, it may be unnecessary to have patients be admitted or provide treatments such as intravenous infusion of tocolytic agents and cervical cerclage simply based on the finding of short cervical length.

In this manuscript, we review the methods to measure cervical lengths and discuss optimal timing for screening examination, implications of cervical length measurement in women at high risk of preterm delivery, and limitations of the cervical length measurement.

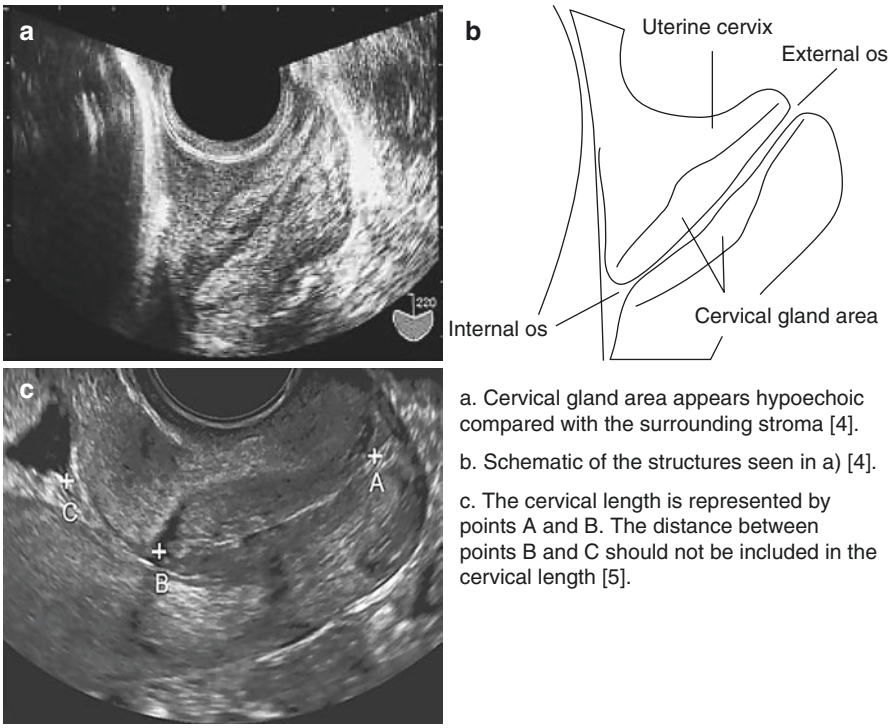
7.2 Measurement of Cervical Length

Table 7.1 summarizes the methods to measure cervical length [3]. The following are important considerations listed in Table 7.1.

1. The lower uterine segment and uterine cervix may deform easily due to the pressure from the surrounding tissues. In particular, pressure from the above may cause the anterior and posterior walls of the lower uterine segment to come in contact. Furthermore, histological internal os of the uterus may appear closed when it is in fact dilated. Therefore, the bladder must be empty.
2. The ultrasound probe should be inserted into the anterior vaginal fornix if possible. However, it may be difficult to do so due to the particular orientation of the cervix or if the cervix is displaced due to the presence of uterine fibroids. It is critical to obtain a longitudinal view of the center of the cervix in order to

Table 7.1 The methods to measure cervical length

Measure cervical length according to the following procedure:
1. Empty the bladder before measuring the cervical length
2. Insert the ultrasound probe into the anterior vaginal fornix, move it sideways, and obtain a longitudinal view of the cervix
3. Identify the internal os (identify the cervical canal and cervical gland)
4. Retract the probe as much as possible while maintaining the view of the cervical canal
5. Adjust the image size so that the cervical canal occupies approximately 50–75% of the image
6. Perform a pressure test and measure the shortest cervical length
7. Measurements should be obtained by manually tracing the structure or by dividing the structure into two segments and measuring the lengths of each segment in straight lines



a. Cervical gland area appears hypoechoic compared with the surrounding stroma [4].

b. Schematic of the structures seen in a) [4].

c. The cervical length is represented by points A and B. The distance between points B and C should not be included in the cervical length [5].

Fig. 7.1 Cervical gland area. (**a**) Cervical gland area appears hypoechoic compared with the surrounding stroma [4]. (**b**) Schematic of the structures seen in (**a**) [4]. (**c**) The cervical length is represented by points A and B. The distance between points B and C should not be included in the cervical length [5]

identify the cervical gland and cervical canal. If these structures are not identified, it would be difficult to identify women with short cervical length. Thus, it is important to image the entire length of the cervical canal.

3. The cervical gland appears hypoechoic (sometimes hyperechoic) in comparison to the surrounding stroma. Cervical length should not include the majority of the closed portion of the uterine isthmus; rather, it should be defined as the length between the external os and the opposite edge (histological internal os of the uterus) where the cervical gland region is visible on TVS (Fig. 7.1) [4, 5].
4. When the ultrasound probe is inserted deep into the vagina and pressure is applied to the cervix, the pressure from the probe may lead to compression as described above in (1). When this occurs, the probe has to be retracted.
5. The ultrasound image should be large enough to encompass the entire structure of the cervix. Accurate assessment is difficult when the image is too small.
6. The cervical length changes periodically due to physiological uterine contraction. Thus, the measurement should ideally be performed over 3–5 min. In fact, we often observe that cervical length shortens during uterine contraction, forming cervical funneling. However, if it is impractical to image for 3–5 min in a

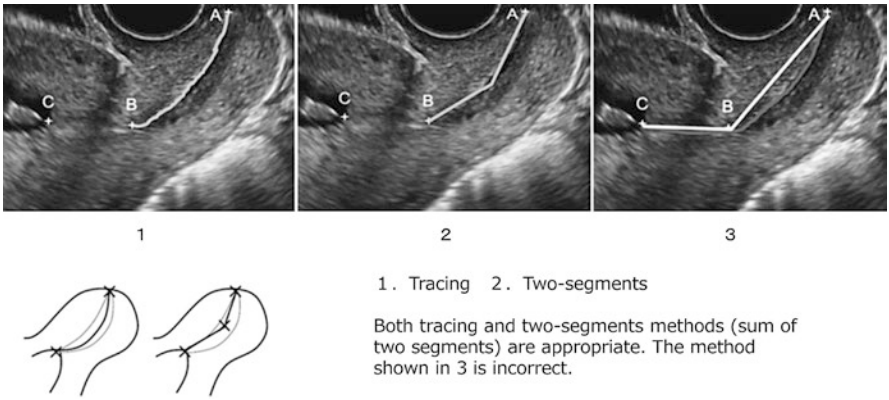


Fig. 7.2 Methods to measure cervical length [6]. (1) Tracing. (2) Two segments. Both tracing and two segments methods (sum of two segments) are appropriate. The method shown in (3) is incorrect

busy outpatient clinic, the examiner can manually replace either the fundus of the uterus downwards (caudal) or suprapubic region outwards (dorsal). This method artificially causes a dynamic change to the cervical canal, mimicking uterine contraction. The pressure should be applied for 20–30 s, and results in a shortening of the cervical length. The measurement of cervical length after dynamic shortening should improve the predictive accuracy for preterm delivery.

7. The cervical canal is curved in many patients. Thus, there will be some errors when the length is measured in a straight line. Instead, measurements should be obtained by manually tracing the structure or by dividing the structure into two segments and measuring the length of each segment (Fig. 7.2) [6]. Measurements may be obtained in a straight line when the cervical canal is shortened. In fact, a study demonstrated that the cervical canal was straight in all cases where it was <16 mm [7].

7.3 Optimal Timing to Screen for Cervical Length

In 1996, Iams et al. used TVS to measure cervical length at around 24 weeks and demonstrated that short cervical length is associated with a risk of preterm delivery at <35 weeks (Fig. 7.3) [2]. Specifically, the relative risks of preterm delivery compared with women with cervical length of over 40 mm were as follows: 1.98 for cervical lengths of ≤40 mm, 2.35 for ≤35 mm, 3.79 for ≤30 mm, 6.19 for ≤26 mm, 9.49 for ≤22 mm, and 13.99 for ≤13 mm. Furthermore, Guzman et al. performed a retrospective study and demonstrated that the measurement of cervical length between 15 and 24 weeks of pregnancy provides important information (Fig. 7.4) [8]. In this study, they demonstrated that women who were suspected of having cervical incompetence had shorter cervical length at around 15th week of pregnancy, and that the trend increased

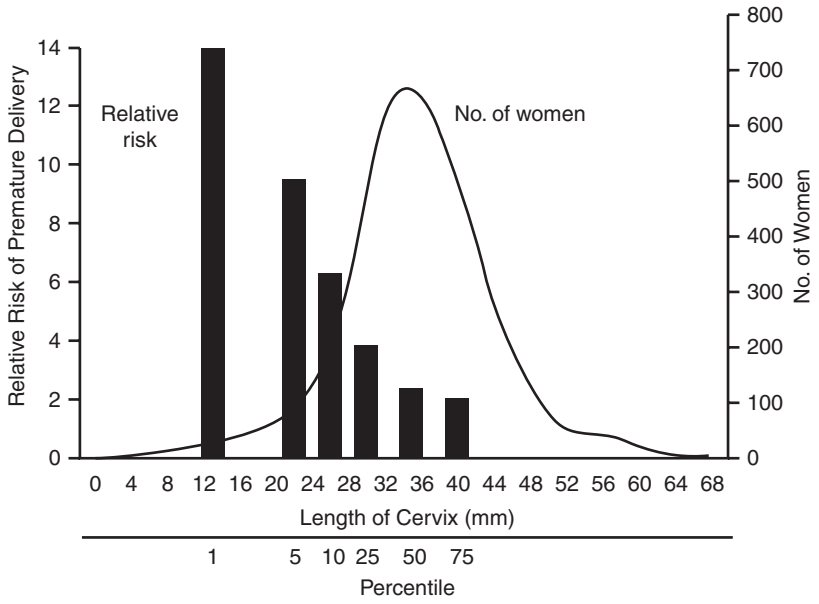


Fig. 7.3 Relative risk of premature delivery by the cervical length [2]

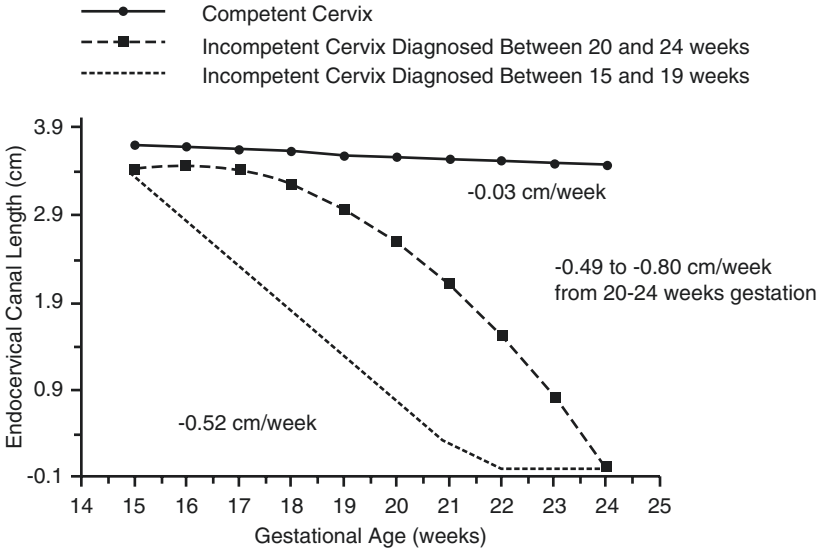


Fig. 7.4 Changes in the cervical length in patients with competent cervix and incompetent cervix (diagnosed between 15–19 weeks and 20–24 weeks) [8]]

significantly over time compared with those without cervical incompetence. There are many other studies to date that demonstrate the association between preterm delivery and cervical length in the second trimester, and the evidence suggests that short cervical length is a sensitive indicator of early-stage preterm delivery.

However, studies suggest that measurement of cervical length during the first trimester of pregnancy may not be informative. Antsaklis et al. performed a large-scale study including over 1000 women and demonstrated that only one of them had cervical lengths of <25 mm between 11 and 14 weeks of pregnancy [9]. In addition, Berghella et al. measured cervical length of 183 women before 14 weeks of pregnancy (10–13 weeks) who were at high risk of preterm delivery and demonstrated that only 5% of them had cervical lengths of <25 mm [10]. With the improved accuracy of ultrasonography systems, the cervical canal can now be imaged clearly during the first trimester to measure cervical length. As such, a recent study demonstrated that the clear distinction of the cervix and isthmus enables accurate evaluation of these structures, such that the measurement of cervical length in the first trimester of pregnancy is in fact useful in predicting preterm delivery [5].

There are few studies that report the usefulness of cervical length screening during the third trimester. In general, the cervical length of women is around 40 mm during the first to second trimester of pregnancy, and shortens to 25–30 mm after 32 weeks [11]. Thus, shortening of cervical length during the late weeks of pregnancy may be considered physiological. There is currently no consensus as to the usefulness of cervical length measurement to predict preterm delivery during this period.

Collectively, current consensus is that screening for cervical length is most optimally performed during the second trimester of pregnancy. Further evidence is required to justify screening for cervical length during the first trimester. Given that various complications including poor suckling, hypoglycemia, and apnea are seen in late preterm infants (born at 34-0/7 to 36-6/7 weeks) [12], it might be necessary to reconsider the value of screening for cervical length during the third trimester of pregnancy.

7.4 Cervical Incompetence

We have reviewed implications of screening for cervical length in women who are at low risk of preterm delivery. This section will focus on cervical incompetence, which poses a risk for preterm delivery.

Cervical incompetence has had various definitions, and there are currently no standard diagnostic criteria. Nevertheless, it is often defined as having indolent dilation of the cervical canal during the second trimester of pregnancy [13]. Risk factors for cervical incompetence include history of miscarriage or preterm delivery during the second trimester due to an unknown cause, as well as having cervical conization and trauma including cervical laceration.

Figure 7.5 illustrates a case of a patient with cervical incompetence. The presence of funneling was observed on ultrasound at 21 weeks. In this case, funneling is characterized by the invagination of the gestation into the cervical canal due to dilation of the internal os. Dilation of the internal os is correlated with the rate of

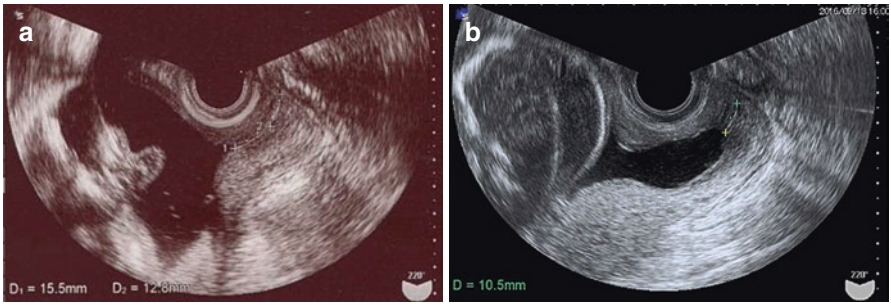


Fig. 7.5 A case of cervical incompetence. The patient was a 30-year-old woman who has had a previous child birth and a cervical conization. During her previous pregnancy, she underwent a prophylactic cervical cerclage and had a natural childbirth at 40 weeks. For this pregnancy, the patient was monitored over time as she did not wish to undergo cervical cerclage. The images represent the (**a**) at 18 weeks (cervical length: 28.3 mm) and (**b**) at 21 weeks (cervical length: 10.5 mm). The patient had a spontaneous rupture of the membrane at 24 weeks, requiring emergency cesarean section. She was unaware of uterine contraction, and cervical incompetence was suspected based on the clinical course

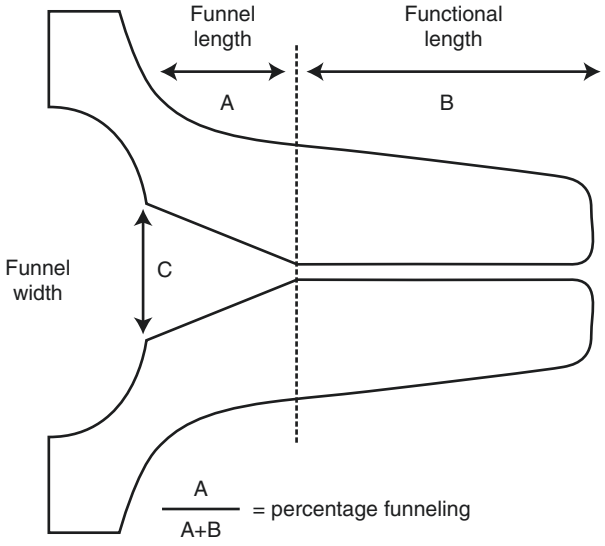


Fig. 7.6 Measurement of cervical length when funneling is present [14]

preterm delivery. According to the study by Berghella et al., preterm delivery rates were 10% in women with funneling of <25% and 70% in women with funneling of over 50% [14]. Figure 7.6 illustrates the method for measuring cervical length in women with dilated internal os. However, a study demonstrated that funneling is not an independent risk factor of preterm delivery, suggesting that the risk should be evaluated by measuring the shortened cervical length including the funneling [15]. In fact, funneling is sometimes observed in women with sufficient cervical length,

and these cases are not associated with an increased risk of preterm delivery. As described above, dynamic changes such as opening and closure of the internal os should be assessed to evaluate the risk of preterm delivery.

7.5 Limitations of Cervical Length Measurements

Romero et al. suggested that preterm delivery has various causes and should be considered a syndrome [16]. Specifically, they suggested that various factors including infections, hormone responsiveness, inflammatory response, environmental factors, lifestyle, and factors associated with the placenta and fetus interact with one another to cause preterm delivery.

Prediction of preterm delivery by cervical length can lead to false positive results in many cases. In addition, an appropriate approach to measure the length for those who present with short cervical length has not been well-established. Thus, there are limitations as to the reliability of the measurement.

The risk of preterm delivery should therefore be evaluated in combination with other methods. They include measurements of neutrophil elastase and fetal fibronectin in the cervical mucosa and concentrations of biochemical markers such as cytokines in the amniotic fluid and cervical mucosa [17, 18], as well as screening for bacterial vaginosis [19].

7.6 Conclusions

Following the study by Iams et al., screening for cervical length in low-risk women has become a common procedure. The procedure is effective to identify women who may be at high risk of preterm delivery. However, it might lead to unnecessary interventions in many cases as it has a low sensitivity for preterm delivery and has a low positive predictive value. Furthermore, the positive predictive value of cervical length measurement is relatively low in women who are at a high risk of preterm delivery. Therefore, cervical length measurement should be combined with other procedures such as measurements of other biomarkers and screening for bacterial vaginosis to improve the prediction of preterm delivery. As there are currently no standard treatment strategies, interventions for short cervical length should be determined in consultation with patients.

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Part III

Other Mechanisms Related to Preterm Labor

Multiple Mechanisms of Preterm Labor Other Than Intrauterine Infection

8

Koutarou Doi

Abstract

The causes of preterm labor and delivery have multiple antecedents and contributing factors. Spontaneous preterm labor with intact fetal membranes more commonly occurs in association with multifetal pregnancy, intrauterine infection, cervical insufficiency, hydramnios, and uterine abnormality. Also, the degree of uterine stretch in cases of multifetal pregnancy, hydramnios, or uterine abnormality affects the course of preterm labor. The risk of preterm labor is known to be increased by several maternal infections (e.g., urinary tract infection) as well as appendicitis and periodontal disease. Maternal infections other than intrauterine infection may cause endotoxin-induced uterine attack leading to preterm labor. Other contributing factors that affect the frequency of preterm labor are several genetic factors, environmental factors, the interval between pregnancies, and prior preterm birth. The latter is one of the most important risk factors for preterm labor: The recurrent risk of preterm delivery is threefold greater for women with a previous preterm delivery than for women whose first delivery was at term. Also, the maternal lifestyle factor of insufficient as well as excessive maternal weight gain increases the risk. This chapter introduces these multiple mechanisms of preterm labor and delivery, with the exception of intrauterine infection.

Keywords

Preterm labor · Multifetal pregnancy · Hydramnios · Uterine abnormalities · Urinary tract infection · Appendicitis · Periodontal disease · Inadequate maternal weight gain · Prior preterm birth

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8.1 Multiple Mechanisms of Preterm Labor and Delivery

Direct causes of preterm births other than maternal or fetal indications are spontaneous preterm labor with intact membranes, idiopathic preterm premature rapture of membrane (PPROM), and twins or higher-order multifetal births. Among preterm births, 40–45% are due to spontaneous preterm labor and 30–35% are due to preterm membrane rupture [1]. More than one in every two twins and more than nine of every ten triplets are born preterm or with low birth weight in the USA [2]. The causes of preterm labor and delivery have multiple antecedents and contributing factors [3]. The common findings associated with spontaneous preterm labor with intact fetal membranes are multifetal pregnancy, intrauterine infection, cervical insufficiency, hydramnios, and uterine abnormalities. Several maternal illnesses including infections (e.g., urinary tract infection), appendicitis, and periodontal disease increase the risk of preterm labor, and several genetic and environmental factors affect the frequency of preterm labor. These wide-ranging factors all lead to premature cervical dilation and effacement and premature activation of uterine contractions [4]. However, the findings of recent animal studies support the notion that preterm birth is not always an acceleration of the normal process. The four major causes of preterm birth are uterine distention, maternal-fetal stress, premature cervical changes, and infection, and the etiology determines which of the various pathways that induce early parturition is activated [4]. In the following sections, we look in more detail at some of the specific antecedents and contributing factors to preterm labor and delivery other than intrauterine infection.

8.2 Multifetal Pregnancy

Twins or higher-order multifetal births account for approximately 3% of neonates born in the USA [2], and preterm delivery continues to be the major cause of the high rates of perinatal morbidity and mortality associated with multifetal pregnancies. Preterm labor affects up to 50% of twin deliveries, 75% of triplet deliveries, and 90% of quadruplet deliveries [5]. Similar to cases of singleton preterm labor, intraamnionic infection is documented in approximately one-third of twin pregnancies [6]. In multifetal pregnancies, the causes of preterm labor are related to the effects of uterine stretch, with early uterine distention thought to act in initiating the expression of contraction-associated proteins in the myometrium [7]. More recent reports suggest that as uterine stretch increases, levels of gastrin-releasing peptides increase and promote myometrial contractility. The influence of uterine stretch on the cervix should also be considered, because premature stretch may be the starting point of events that accelerate the timing of uterine activation, including cervical ripening [4].

8.3 Hydramnios

Hydramnios is an abnormal increase in amniotic fluid volume that complicates 1–2% of pregnancies [8]. Its underlying causes include fetal anomalies in

approximately 15% of cases and diabetes in 15–20%. Although a diagnosis of exclusion, idiopathic hydramnios accounts for up to 70% of hydramnios cases. Maternal symptoms typically appear only when hydramnios is severe or develops rapidly: Acute hydramnios tends to develop earlier in pregnancy and may cause preterm labor, whereas the gradual accumulation of excessive abdominal distention in chronic hydramnios tends not to cause much discomfort [4]. The causes of preterm labor in hydramnios are related to the effect of uterine stretch as well as to multifetal pregnancy [4].

8.4 Uterine Abnormalities

The population-based prevalence of congenital uterine abnormalities is 0.4–10%, but these abnormalities occur at a significantly higher rate in woman with recurrent miscarriage [9]. In the general population, the most common finding is arcuate uterus, followed in order by septate, bicornuate, didelphic, and unicornuate uterus. These Mullerian anomalies carry significant obstetric risks, including first- and second-trimester miscarriage, malpresentation, fetal-growth restriction, fetal demise, prematurity, ruptured membranes, and preterm delivery [10]. The causes of preterm labor in cases of uterine abnormality are also related to the effect of uterine stretch and to multifetal pregnancies [4].

8.5 Maternal Infections Other Than Intrauterine Infection

Several maternal infections increase the preterm labor risk. Endotoxins released in bacterial infections readily stimulate myometrial contractility. Also, other mechanisms may allow bacteria into the intrauterine cavity during pregnancy: there may be ascending infection, retrograde flow of infection into the peritoneal cavity via the fallopian tubes, or transfer of maternal systemic infection via the placenta [11].

8.5.1 Urinary Tract Infections

Urinary tract infections are the most common bacterial infections seen in pregnant women. Almost all urinary tract infections are due to ascending infection by bacteria in the normal vulvar flora. Most urinary tract infections present as asymptomatic bacteriuria without significant symptoms, but they can sometimes cause clinical infections such as cystitis and pyelonephritis. Several studies have investigated whether asymptomatic bacteriuria affects maternal and fetal perinatal outcomes. Although there is no consensus yet, the results of some studies suggest that asymptomatic bacteriuria is associated with preterm delivery and low birth weight [12]. Acute pyelonephritis is one of the most important bacterial infections encountered in pregnant patients and can sometimes become serious. Endotoxins induce uterine contractions, but most infections are transient and most begin resolving with fluid replacement and antibiotics [13]. Tocolytic therapy for

pregnant women with pyelonephritis should be selected carefully because beta agonists can cause pulmonary edema associated with vascular hyperpermeability in these patients [14].

8.5.2 Appendicitis

Diagnosis of appendicitis is much more difficult in pregnant women than non-pregnant women. This is because the cardinal symptoms of appendicitis, nausea and vomiting, are difficult to differentiate from symptoms caused by uterine enlargement during a normal pregnancy, and the enlarged pregnant uterus can shift the position of the appendix [15]. However, many studies have shown that peritonitis caused by appendiceal perforation is associated with very poor maternal and fetal outcomes. Therefore, it is important to quickly initiate surgical treatment when appendicitis is suspected even if a definitive diagnosis has not been reached [16]. Appendicitis during pregnancy is known to increase the risk of miscarriage and preterm delivery. This risk is even more pronounced when peritonitis occurs due to appendiceal perforation. In a large study of 908 pregnant women with appendicitis, rates of preterm delivery and low birth weight were 1.5–2 times higher in the appendicitis group than in the control group [17].

8.5.3 Periodontal Disease

Several recent studies have noted an association between periodontal disease and preterm delivery [18]. Offenbacher et al. found that the rate of preterm delivery was about seven times higher in pregnant women with periodontal disease than in those without periodontal disease [19]. Hauth et al. found that 24 of 28 pregnant women who delivered at 32 weeks or earlier had periodontal disease, and their rate of preterm delivery was four times higher than that in pregnant women without periodontal disease [20]. Research indicates that this could be due to the association between intraoral bacteria, particularly *Fusobacterium nucleatum* and *Capnocytophaga* species, and upper reproductive tract infection. There is no consensus regarding the effect of periodontal disease prevention on preterm delivery. A meta-analysis of prevention and treatment of periodontal disease showed a reduced rate of preterm delivery, but a randomized controlled trial showed no significant difference [21].

8.6 Lifestyle Factors

Inappropriate gestational weight gain is known to be a lifestyle factor that increases the risk of preterm delivery [22]. Other maternal lifestyle factors that have been implicated in preterm delivery include smoking, young age, old age, poverty, and short height. There are varying opinions regarding whether working conditions

during pregnancy are associated with preterm delivery, but one study showed that working more than 40 h a week in a job that requires standing for long periods increases the rate of preterm delivery [23]. Systems for predicting preterm delivery based on combinations of these risk factors have been devised, but none has been found effective to date.

8.7 Genetic Factors

For some time, the hypothesis that genetic factors are involved in preterm delivery has frequently been proposed. The findings that preterm delivery tends to recur, patients can have a family history, and incidence differs between races support this hypothesis. Several studies on the association between mutations and preterm delivery have been published over the past several years especially [4].

8.8 Interval Between Pregnancies

It has been known that a short interval between pregnancies is associated with the rate of preterm delivery in patients with a history of preterm delivery. Recent studies have shown that the interval between pregnancies is associated with poor perinatal outcomes regardless of history of preterm delivery. A meta-analysis from 2006 showed that the risk of preterm delivery or low birth weight increases when the interval between pregnancies is <18 months or more than 59 months [24].

8.9 Prior Preterm Birth

The most important risk factor is a history of preterm delivery. Prior preterm delivery during the second trimester in particular is strongly correlated with preterm delivery in the next pregnancy, as it increases risk by six to eight times. A study of 16,000 deliveries at Parkland Hospital showed that pregnant women with a history of preterm delivery had a threefold higher risk of preterm delivery of the next pregnancy than those who previously delivered at term. In addition, more than one-third of pregnant women with two prior preterm deliveries had a preterm delivery in the next pregnancy [4, 25]. A retrospective study conducted by Ananth et al. in 2006 that investigated outcomes of the next pregnancy after preterm delivery in about 150,000 deliveries showed that the rate of spontaneous preterm delivery of the next pregnancy was 3.6 times higher in women with a prior spontaneous preterm delivery [26]. Risk of recurrent preterm birth is influenced by three factors: the frequency of prior preterm deliveries, severity as measured by gestational age, and the order in which the prior preterm delivery occurred [27]. Thus, an individual woman's risk for recurrent preterm birth is influenced by her past number and term births.

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Abruption and Preterm Labor

9

Seishi Furukawa

Abstract

Placental abruption accounts for 5–10% of all preterm deliveries and is more common in cases involving a lower gestational age. The incidence of placental abruption is highest at earlier gestational age (7–18%, 24–30 weeks of gestation) and then decreases and reaches <1.0% around 36 weeks.

Cigarette smoking, parity (grand multiparity), hypertensive disorders, and preterm premature rupture of membranes are found to be independent factors associated with the development of preterm placental abruptions. In the late preterm period, prognosis tends to deteriorate especially in cases of placental abruption preceded by hypertensive disorders. Furthermore, preceding clinical manifestations such as preterm premature rupture of membranes or hypertensive disorders may not have less of an influence on prognosis at the early preterm period. An understanding of the etiology involving the development of placental abruption, its frequency, and its effect on prognosis should lead to better management of preterm labor.

Keywords

Preterm birth · Placental abruption · Inflammation pathway · Ischemic pathway

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9.1 Introduction: Placental Abruption as a Phenotype of "Placental Bed Disorders" or "Placental Insufficiency"

Recently, a new concept pertaining to the etiology of obstetrical complications was introduced, and is referred to as "placental bed disorders or placental insufficiency" [1, 2]. Extravillous trophoblasts in the first trimester are highly invasive and usually replace endothelial cells lining the walls of spiral arteries. This physiological transformation of spiral arteries is referred to as "spiral artery remodeling" and allows for adequate blood supply to the placenta and optimal oxygen and nutrient delivery during development [3]. The failure of spiral artery remodeling is regarded as a fundamental pathology that can lead to the development of "placental bed disorders" or "placental insufficiency." It was traditionally thought that failure of spiral artery remodeling could lead to preeclampsia and fetal growth restriction; however, it has now been revealed that failure of spiral artery remodeling is associated with more common obstetric disorders including spontaneous abortion, preterm labor with intact membrane, and pre-labor rupture of membranes [4–6]. Placental abruption is also categorized as a subtype of placental bed disorder. It is thought that placental abruption is partially caused by the ischemic pathway in which decidual necrosis, infarction, and vascular dysfunction including failure of spiral artery remodeling are involved [7–9].

In the first place, preterm birth is a consequence of multifactorial factors. In fact, one-third of preterm births <37 weeks of gestation is due to preeclampsia and intrauterine growth restriction [10]. In other words, placental bed disorders account for one-third of premature deliveries. On the other hand, the remaining two-thirds are caused by spontaneous premature births. Placental ischemic lesions in decidua are more commonly seen in the group comprising preterm labor with intact membranes. Specifically, there is a higher percentage of spiral artery remodeling failure in the group comprising preterm labor with intact membrane (13.1%) than the group comprising normal term delivery (3.6%), according to reports by Kim et al. [6]. Interestingly, placental abruption is frequently seen in the group comprising preterm labor [11]. Those observations suggested that the involvement of "placental bed disorders" or "placental insufficiency" in preterm birth is more common than previously thought. In the past, it was thought that preterm labor is mainly caused by intra-amniotic infection. However, antenatal antibiotic treatment for preterm labor often failed to seize preterm labor [12]. Intra-amniotic infection is less frequently seen by amniocentesis in women with preterm labor and intact membranes [13]. These facts suggest that infection alone is not the ultimate cause of preterm births. Therefore, it is important to understand preterm births from the viewpoint of the phenotype of "placental bed disorders" or "placental insufficiency."

Of course, placental abruption is also caused by the inflammation pathway, in that chorioamnionitis is more commonly involved in cases comprising placental abruption with preterm birth [14]. Consequently, placental abruption is also a consequence of multifactorial causal factors. An understanding of the etiology involving the development of placental abruption should lead to better management of preterm labor.

9.2 Incidence of Placental Abruption in Preterm Period

Generally, placental abruption (abruption) occurs in approximately 1% of all pregnancies [15]. It is also well known that women diagnosed with abruption have a four to sixfold increased risk of a preterm delivery [16].

In Japan, placental abruption accounts for 4.7% of all preterm deliveries from 30 weeks of gestation to 36 weeks of gestation [17]. Furthermore, 60% of placental abruptions occur in preterm, while the remaining 40% occur in term deliveries [17]. In fact, it is reported that the number of placental abruptions is almost equivalent in term and preterm births [18]. According to a hospital-based retrospective cohort study in Taiwan, placental abruption accounts for 9.9% of all preterm deliveries <34 weeks of gestation [19]. Ananth et al. reported that placental abruption accounts for 10% of preterm births in the USA [16]. In Israel, placental abruption complicates 5% of all preterm deliveries [20]. Accordingly, placental abruption accounts for 5–10% of all preterm deliveries. However, from the perspective of a histological study, the occurrence of placental abruption increases further among preterm births. According to a report by Garmi et al., the incidence of histological signs of placental abruption accounts for 18% of preterm births between 23 and 36 weeks of gestation [21].

Placental abruptions are more common in cases involving a lower gestational age and the occurrence differs according to gestational age. In Japan, the frequency of placental abruption in the periods from 30 to 33 weeks is 6.7%. The frequency then decreases linearly as gestational age progresses, and reaches 0.9% at 37 weeks of gestation [17]. Similar trends are recognized in Israel and the USA. Oyelese reported that the incidence of placental abruption is highest (9%) at 24–26 weeks of gestation and then linearly decreases toward the term [22]. Pariente et al. reported that the incidence of placental abruption is highest (12–18%) at earlier gestational age (24–30 weeks) and then decreases and reaches 0.9% at 37 weeks [23]. Although there are some differences in the occurrence of placental abruption according to gestational age, there is no doubt that its frequency increases at mid-pregnancy and then sharply decreases thereafter. Thus, the high incidence of premature delivery with placental abruption is an important issue in perinatal care.

9.3 Background of Placental Abruption in Preterm Labor

Generally, maternal age, parity, hypertensive disorders, cigarette smoking, oligohydramnios, polyhydramnios, chorioamnionitis, and preterm premature rupture of membranes (PPROM) are well-known risk factors [22, 23]. The same common risk factors are also observed for placental abruption in preterm births. According to a study that examined the background only for placental abruption in preterm births, parity (grand multiparity) and hypertensive disorders (severe pregnancy-induced hypertension) were found to be independent factors [20]. Another study showed that placental abruption in preterm births is associated with cigarette smoking, hypertension, intravenous drug abuse, and a history of recent abdominal trauma [24]. Among

hypertensive disorders, superimposed preeclampsia on chronic hypertension is highly associated with placental abruption in preterm births. Furthermore, the duration of premature rupture of membranes is significantly associated with placental abruption in preterm births [24]. It is interesting to note that few antenatal visits and malpresentation are noted as independent risk factors for placental abruption in preterm births [20, 24].

Women with PPROM have a higher risk of developing placental abruption throughout gestation [18]. Within preterm births, the incidence of inflammatory manifestation including PPROM without fever, PPROM with fever, and fever without PPROM is higher in women with placental abruption than those without (relative risk: 1.38). That was 1.39 at term birth. Instead, the incidence of chronic manifestation including chronic hypertension, pregnancy-induced hypertension, small for gestational age, diabetes, and smoking among preterm births is higher in women with placental abruption than those without (relative risk: 1.87). That was 2.37 at term birth [18]. Thus, placental abruptions preceded by inflammatory manifestation are frequent among preterm births, while placental abruptions preceded by chronic manifestation are more frequent among term births. On the other hand, one report from Norway showed that women with PPROM have a lower risk of placental abruption between 29 and 37 weeks of gestation [25]. During the relatively early preterm period of <30 weeks gestation, inflammatory manifestation may be strongly involved in the development of placental abruption.

There is a risk of recurrence of placental abruption in subsequent pregnancies [26]. According to Ruiter et al., women who experienced placental abruption at term gestation are at greater risk of recurrence than women who experienced placental abruption at preterm gestation [27]. It is important to determine the trend of this recurrence since it is difficult to predict the onset of placental abruption.

It has been known that there are racial differences regarding risk factors for preterm birth [10]. Racial difference is also observed in the occurrence of preterm birth with placental abruption. According to Shen et al., the risk of placental abruption resulting in preterm birth is lower for black mothers compared with white mothers. On the other hand, the risk of placental abruption resulting in term birth is greater for black mothers compared with white mothers [28].

9.4 Pathological Aspect of Preterm Placental Abruption

The findings of placental pathology in cases of preterm birth with placental abruption differ from that of term births. Examination of placental histopathology in the extremely low birth weight (<1000 g, 23–30 weeks of gestation) showed histological chorioamnionitis in 56% of placental abruptions. Histological chorioamnionitis and funisitis are more frequently observed in placental abruptions in preterm births compared with preterm births with iatrogenic early delivery for obstetrical indications [29]. On the other hand, there is no evidence of histological chorioamnionitis

of placental abruption with term gestation [29]. As mentioned for the background of placental abruption in preterm labor, PPROM is frequent among preterm placental abruption, while chronic hypertension, pregnancy-induced hypertension, and small for gestational age are more frequently observed in term placental abruption [18]. These pathological observations are consistent with clinically obtained findings as inflammatory phenomena are strongly involved in the development of placental abruption at the early preterm period.

As mentioned in the Introduction, placental abruption is also categorized as a subtype of "placental bed disorders." In 12 cases of placental abruption that underwent placental site biopsy, the failure of spiral artery remodeling was observed in seven cases [8]. The failure of spiral artery remodeling is a fundamental pathology associated with the development of preeclampsia and fetal growth restriction, suggesting that those conditions have a common causal factor. However, ischemic changes of placenta do not appear to be as relevant in preterm births with placental abruption. The incidence of ischemic changes does not differ between preterm births with placental abruption (22–26 weeks) and preterm births without placental abruption [30]. Instead, the incidence of hemosiderin deposition is significantly higher in preterm births with placental abruption (22–26 weeks) compared with preterm births without placental abruption [30]. Deposition of hemosiderin is also evidence of placental bleeding and is an important finding when considering the cause of premature birth [31]. However, the most popular ischemic lesion associated with all placental abruptions is placental infarctions [9].

9.5 Mechanism Leading to Preterm Birth in Preterm Placental Abruption

There is no doubt that placental hemorrhage including first-trimester vaginal bleeding, placental abruption, microscopic and gross placental hemorrhage is attributed to preterm delivery [32]. It is thought that pathologies that lead to placental abruption precede hemorrhage and are related to inflammation and ischemic processes. As discussed in relation to the pathological aspect of preterm placental abruption, inflammation-related pathological findings in particular are often observed in preterm birth with placental abruption.

Activated neutrophils and macrophages accumulate in the decidua in cases of chorioamnionitis, and produce matrix metalloproteinases. Increased production of matrix metalloproteinases in the decidua is thought to comprise a normal process during labor, and is a process which is thought to facilitate placental detachment after parturition [33]. Therefore, increased production of matrix metalloproteinases could promote premature detachment of the placenta, that is, preterm placental abruption [18]. However, there is a difference in degree of detachment of the placenta. Such hemorrhage also induces thrombin production in the decidua, which plays an important role in the development of PPROM by acting through

protease-activated receptors to produce pro-inflammatory cytokines and matrix-degrading metalloproteinases [34–36]. Thrombin also induces apoptotic activity followed by decidual bleeding [37, 38], and inhibits the progesterone receptor, thus attenuating the effect of progesterone followed by preterm labor [39]. Moreover, thrombin itself has the ability to contract the myometrium of the uterus [40, 41]. The aforementioned series of reactions is thought to result in preterm birth.

9.6 Effect of Preterm Placental Abruption on Perinatal Outcome

Placental abruption is a major cause of poor perinatal outcome [16, 42]. However, the mortality rate of placental abruption in preterm births seems not to differ all that greatly from other clinical presentations in preterm births. According to a population-based cohort study of 3138 singleton preterm births from 24 to 34 weeks of gestation, the mortality rate in cases of placental abruptions did not differ from that of threatened preterm labor, PPROM, pregnancy-induced hypertension (PIH) without fetal growth restriction (FGR), PIH with FGR, or FGR without PIH [43]. On the other hand, in the late preterm period at around 34 weeks, placental abruptions preceding hypertension had a significantly higher incidence of FGR, intrauterine fetal death, and low fibrinogen level of the mother. Placental abruptions preceding threatened premature labor or PPROM have less severe diseases [11]. Thus, in the late preterm period, the preceding clinical presentation of placental abruption may have more influence on the prognosis, and may not have less influence at the early preterm period.

Does the mortality rate due to early preterm placental abruption change according to gestational age? Ananth et al. showed that gestation-specific perinatal mortality rates were similar between abruption and non-abruption births <28 weeks of gestational age [44]. Furukawa et al. also reported that placental abruption is associated with a risk for the development of non-reassuring fetal status and chronic lung disease in infants born between 22 and 26 weeks of gestation, but showed no effect on neonatal mortality [30]. Infants born after placental abruption between 22 and 31 weeks of gestation have a higher risk of grade 3 and 4 intraventricular hemorrhage [45]. These reports suggest that extreme immaturity is a major contributing factor for perinatal mortality in cases of placental abruption with a gestational age of <28 weeks. Nevertheless, placental abruption increased the neonatal morbidity of extremely premature infants.

Preterm placental abruption is often mistaken for premature labor, and sometimes a tocolytic agent such as ritodrine hydrochloride is administered. According to Ogawa et al., tocolytic therapy is a factor involved in exacerbation of the neonatal prognosis in preterm placental abruption [46]. It is therefore necessary to carefully consider the use of tocolytic therapy with ritodrine hydrochloride for impending preterm birth. However, in most countries ritodrine hydrochloride is not used as the first drug of choice for seizing premature labor.

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Part IV

Prevention, Treatment, and Management

10 Prevention and Tocolytic Agent: Hydration, Bed Rest, Ritodrine, and Special Comments on Long-Term Tocolysis

Yoshio Matsuda

Abstract

Although the diagnosis of preterm labor (PTL) is not always easy, the treatment option of PTL depends on gestational age at diagnosis, degree of emergency (genital bleeding, cervical dilatation, and the presence of painful uterine contraction), need for maternal transfer, and so on.

Keywords

Ritodrine · Long-term tocolysis · Short-term tocolysis · Bed rest

10.1 Hydration and Bed Rest

Hydration method for PTL is described as follows: an indwelling catheter is placed in an arm vein, and Ringer's lactate solution is infused at an initial rate of 500 mL for the first 30 min, followed by a rate of 200 mL/h. This classical hydration method has now been proved ineffective, as shown in Cochrane Database of Systematic Review 2002 [1].

Traditionally, bed rest has been thought to provide benefits to both the pregnant woman and her baby. Hypothesized benefits include increasing uterine blood flow, relieving pressure on the cervix, and improving placental transfer of nutrients. The potential harms of bed rest include an increased risk of venous thrombosis, pulmonary embolism, bone demineralization, and negative psychosocial effects [2–5]. Hypothesized hazards include the possibility of increased elective preterm delivery to end a situation that could be becoming intolerable to the woman.

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Levin et al. did secondary analysis of the Maternal Fetal Medicine Units network (MFMU)'s Preterm Prediction Study; a multicenter prospective cohort study [6]. Of the 1086 women that met the inclusion criteria: patient reported contractions, severe back pain, a cervical length <15 mm, spotting, protruding membranes, or positive fetal fibronectin, 16.5% ($n = 179$) delivered preterm. 9.7% ($n = 105$) of women were recommended activity restriction (AR), with 37.1% ($n = 39$) having a preterm birth. In the group not recommended AR ($n = 981$), 14.3% ($n = 140$) delivered preterm and concluded that the activity restriction was associated with an increased risk of PTB and the use of AR in this population should be discouraged.

As such, antenatal hospitalization for bed rest has not been shown to decrease the rate of preterm birth or to improve perinatal outcome. It may have adverse effects on women, and should be avoided wherever possible.

10.2 Ritodrine and Special Comments on Long-Term Tocolysis

Women who present with signs and symptoms of labor frequently will not deliver in the short term and many will continue to full term, even in the absence of interventions. Women with risk factors will usually not deliver preterm. Conversely, even women who receive prophylactic interventions may still deliver early.

The diagnosis of preterm labor generally is based on clinical criteria of regular uterine contractions accompanied by a change in cervical dilatation (at least 2 cm), effacement, or both. Although tocolysis have not shown to improve perinatal outcome, their use can rely on achieving two goals: (1) to gain time for antenatal corticosteroids administration to become effective; (2) to gain time to allow in utero transfer to a hospital with intensive care and newborn intensive care units.

Currently licensed drugs for tocolysis in Japan include beta-agonists and magnesium sulfate [7, 8]. There is no evidence about advantage of one tocolytic drug in comparison with others in prolongation of pregnancy [9–11].

In this chapter, I focus on betamimetics, especially ritodrine hydrochloride (ritodrine). Betamimetic agents or β-agonists are probably the most widely used tocolytics in preterm labor [12]. All betamimetic agents are chemically and pharmacologically related to the catecholamines, and all act by binding to β-receptors that are present on cell membranes in the uterus and in many organs throughout the body. The occupation of β-receptors activates adenylate cyclase through a guanine nucleotide regulatory protein to convert adenosine 5′-triphosphate to cyclic adenosine 3′,5′-monophosphate (cAMP). It then acts as an intracellular messenger. Increase in cAMP relaxes smooth muscle. Stimulation of β-receptors is responsible for actions such as an increase in heart rate and stroke volume, relaxation of intestinal smooth muscle, and lipolysis. Also β-stimulation mediates glycogenolysis and relaxation of smooth muscle in the arterioles, the bronchi, and the uterus. It has been known for some time that continuous

Table 10.1 Protocol and contraindication

Protocol	Begin intravenous infusion at 50 μg/min, and increase by 50 μg/min every 20 min until contraction frequency is six or fewer per hour, or maximum dose of 200 μg/min is reached or when mother heart rate exceeds 120 beat per minute
Contraindication	*Maternal*: Significant hypertension (eclampsia, severe pre-eclampsia, chronic hypertension), cardiac disease, uncontrolled diabetes, hyperthyroidism (thyrotoxicosis), closed-angle glaucoma, maternal bleeding with hemodynamic instability, any medical or obstetric condition that contraindicates prolongation of pregnancy, hypersensitivity to a tocolytic agent, advanced dilatation/effacement, clinical chorioamnionitis *Fetal*: Gestational age ≥37 weeks, (estimated) birth weight ≥2500 g, intrauterine fetal demise or lethal anomaly, in utero fetal compromise (nonreassuring fetal status, FGR)

administration of betamimetic agents results in a loss of efficacy. This is attributed to down-regulation of the β-receptors and desensitization of the adenylate cyclase activity.

Protocol and contraindication of ritodrine are shown in Table 10.1 [13, 14]. As betamimetic drugs are powerful agents with adverse effects that are related to the dose administered, this would seem to be undesirable. It has, therefore, been proposed to lower the infusion rate as soon as uterine inhibition is achieved to a level that is sufficient to maintain uterine inhibition.

Heart frequency (every 15 min), breath frequency (lung auscultation, every 4 h), blood pressure (every 15 min), and liquid balance (income and expenditure) must be controlled. If thoracic pain or arrhythmia appears we must do an electrocardiogram and stop the perfusion, because a heart attack may happen [15, 16].

Another serious complications, some of which require termination of pregnancy, have also been reported with the use of betamimetic agents, including acute lung edema [17], cardiomyopathy [18], parotid pain [19], and neutropenia [20].

In order to prevent lung edema, we will reduce sodium chloride intake and liquid volume. The onset of rhabdomyolysis is known to be a rare, but serious adverse reaction to tocolytic therapy [21]. We have treated a patient who developed rhabdomyolysis after 5-week administration of ritodrine hydrochloride in combination with magnesium sulfate (MgS04) in a twin pregnancy [22]. In this case, a significant increase of creatine kinase (CK) was observed. The CK leve1 is the most sensitive and widely used marker for skeleto-muscular disorders. However, numerous unknowns remain concerning the background and the risk factors for the onset of rhabdomyolysis during tocolytic therapy [23].

These tocolytic drugs penetrate through placenta barrier and can cause fetal tachycardia and hypoglycemia, in some cases hyperinsulinemia after birth. They are not indicated for prolonged treatment due to significant cardiotoxic effect. Maternal and fetal/neonatal side effects are shown in Table 10.2 [14].

Table 10.2 Maternal and fetal/neonatal side effects

(Maternal) Tachycardia, arrhythmia, pulmonary edema, cardiac ischemia, hypotension, hyperglycemia, rhabdomyolysis, agranulocytosis, hypokalemia, tremor, nausea, vomiting, chest pain, jitteriness, pruritus
(Fetal/neonatal) Tachycardia, hyperinsulinemia, hypoglycemia, cardiac hypertrophy, cardiac ischemia, hypocalcemia, hypotension, intraventricular hemorrhage

Table 10.3 Effectiveness of various tocolytic therapies vs. placebo

Tocolytic or tocolytic category	48 h	7 days	PTB <37 weeks	Perinatal mortality
Betamimetics	Yes	Yes	No	No
Magnesium sulfate	No	N/A	No	No
COX inhibitors	No	N/A	Yes	No
Calcium channel blockers	Yes	N/A	Mixed[a]	N/A
Oxytocin receptor antagonists	No	N/A	No	No
Nitric oxide donors	No	N/A	N/A	No

Abbreviation: *N/A* not available, as not evaluated in randomized controlled trials
[a]One trial showed benefit, while another did not, with data not feasible for meta-analysis

10.3 Results of RCTs and Meta-Analysis

Ritodrine and terbutaline have been studied in several randomized placebo-controlled trials. A 2014 meta-analysis included 20 trials; 12 of these compared betamimetics with placebo. Preterm delivery within 48 h and within 7 days was less common among women administered betamimetics (Table 10.3). However, there was no evidence of a reduction in PTB <37 weeks. Additionally, betamimetics did not improve perinatal morbidity or mortality. Maternal side effects are significant [24].

Intravenous ritodrine is no longer marketed in the USA. In 2011, the U.S. Food and Drug Administration issued a warning regarding terbutaline use. Specifically, it stated that injectable terbutaline should not be used in pregnant women for prolonged treatment (48–72 h) of preterm labor in either the hospital or outpatient setting because of potential for serious maternal heart problems and death [25].

10.4 Long-Term Tocolysis Vs. Short-Term Tocolysis

As mentioned above, the concept of "short-term tocolysis" has been accepted as "48 h," which is enough to gain time for antenatal corticosteroids to become effective, and to gain time to allow in utero transfer to a hospital with intensive care and neonatal intensive care units (NICUs). On the other hand, that of "long-term tocolysis" varies among reports.

Hill et al. [26] reported the outcome of 16 patients treated by continuous long-term intravenous β-sympathomimetic tocolysis (≥1 week's intravenous therapy). Half of the patients received such therapy for at least 5 weeks. Intravenous tocolysis was adjusted to decrease uterine activity and maintain a satisfactory pulse and blood

pressure. Parenteral tocolysis was continued until there was a successful transition to oral therapy, until fetal maturity, or until maternal/fetal indications for delivery were noted. Data indicate that the cardiovascular and metabolic effects were pronounced mostly during the first 3–4 days of therapy and then returned toward pretreatment values. No patients discontinued the treatment because of drug-related problems, electrocardiogram changes, chorioamnionitis, or fever. From this experience, they indicated that, in a selected group of patients and under close supervision, continuous long-term intravenous β-sympathomimetic tocolysis may be considered a safe therapeutic modality able to prolong pregnancy with a more desirable outcome.

Dudley et al. [27] administered intravenous magnesium sulfate tocolysis, either alone or in combination with other tocolytics, to 111 women as follows: (1) 60 (54%) received the drug for 3 or fewer days (short-term group); (2) 29 (26%) received the drug for 3–10 days (intermediate group); and (3) 22 (20%) received the drug for 10 days or longer (long-term group). They reported that side effects (ileus and/or constipation, visual blurring, headache) were more common in the intermediate and long-term groups, but no life-threatening complications were seen and that the drug was discontinued because of side effects in 7% of the patients in each group. They concluded that there need be no time limit on IV magnesium sulfate and that magnesium sulfate tocolysis may be continued as clinically indicated.

Takagi and Satoh [28] performed the retrospective study to evaluate whether long-term (>2 days) tocolysis is effective in treating threatened premature labor. A total of 1147 patients were grouped according to whether or not tocolysis were given, and according to the route of administration and whether or not ritodrine or other tocolytic was given. They reported that prolongation of gestation was significantly longer on patients treated with tocolysis for >2 days compared with the unmedicated, bed-rest group and that IV ritodrine (86% of cases) was considered safe and effective for prolonging gestation in cases of threatened premature labor (Fig. 10.1).

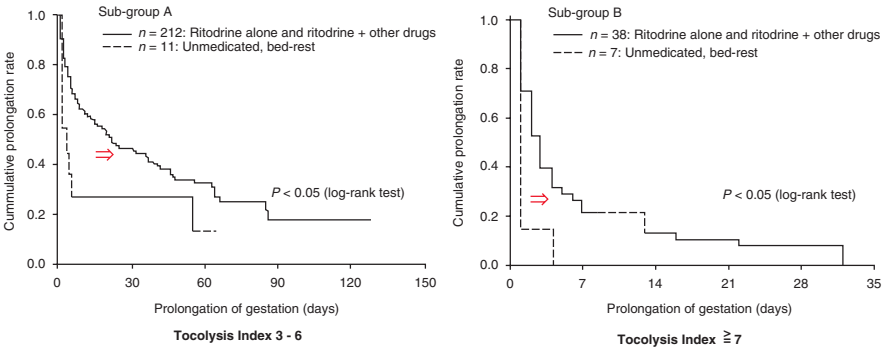

Fig. 10.1 Cumulative prolongation of gestation among patients with threatened premature labor who were admitted to hospital before gestation week 32 and had a tocolysis index score of 3–6 (sub-group A) and scores ≧ 7 (sub-group B) and were treated with IV ritodrine alone and IV ritodrine plus other drugs (magnesium sulfate, terbutaline, indomethacin, and urinastatin), compared with unmedicated, bed-rest patients

Contrary to "primary tocolysis," which is intended for use as soon as the initial diagnosis of true preterm labor is made, maintenance tocolysis is defined as tocolysis used on a woman with a resolved episode of preterm labor, also called "arrested" preterm labor. In such cases, prolonged oral or subcutaneous medications such as terbutaline, ritodrine, and nifedipine were administered as long as 34–36 weeks' gestation, in some cases, by intravenous administration.

Although long-term tocolysis or maintenance tocolysis is used comparatively to "short-term tocolysis," definitive definition of these words is not made. At present, we may regard these words, when the duration of tocolysis extends over 48 h. Because there have been few reports concerning the disadvantage of "long-term tocolysis" and NICUs have been not enough for a long time in Japan, tocolysis has been used usually over 48 h for the purpose of prolongation of pregnancy.

Recently, a historical cohort study was performed in a single center in Japan [29]. The maternal characteristics, frequency of preterm labor, and prescribed dose of tocolytic agents were compared before and after changing the management protocol for threatened premature delivery. They showed that a total of 1548 deliveries were carried out before changing the protocol for the use of tocolytic agents for threatened premature delivery and 1444 deliveries afterwards. The total number of ritodrine hydrochloride ampules used was reduced from 4654 to 514, and the total vials of magnesium sulfate used were reduced from 1574 to 193, but perinatal outcomes such as rate of preterm birth, neonatal weight, and rate of NICU hospitalization were not different between the groups (Table 10.4). From these observations, they

Table 10.4 Neonatal outcome

		Management protocol for preterm labor		
		Old protocol (n = 1548) Mean ± SD, n (%) or median (range)	New protocol (n = 1444) Mean ± SD, n (%) or median (range)	P-value
Delivery (weeks of gestation)		38 ± 3	38 ± 3	0.975
Gestational age at diagnosis of preterm labor (weeks)		26 ± 5	28 ± 4	0.221
Admission due to preterm labor		65 (4.2)	42 (2.9)	0.062
Duration of hospitalization due to preterm labor (days)		44 ± 37	34 ± 30	0.117
Preterm birth (<37 weeks)		182 (11.8)	153 (10.6)	0.324
Preterm birth (<28 weeks)		20 (1.3)	17 (1.2)	0.869
pPROM		57 (37%)	41 (2.8%)	0.217
Preterm delivery due to preterm labor		29 (1.9)	20 (1.4)	0.316
Prolonged gestational days from admission		54 ± 37	48 ± 34	0.432
Male		815 (52.6)	726 (50.3)	0.200
Neonatal bodyweight (g)		2855 ± 575	2868 ± 585	0.542
Apgar score	1 min	8 (0–10)	8 (0–10)	0.634
	5 min	9 (0–10)	9 (0–10)	0.543
Admission to NICU		137 (8.4)	129 (8.5)	0.488
Duration of hospitalization in NICU (days)		59 ± 42	60 ± 35	0.632

NICU neonatal intensive care unit, *pPROM* preterm premature rupture of membranes

concluded that long-term tocolysis in patients with threatened premature delivery should be restricted to prevent maternal and fetal adverse side effects.

10.5 Conclusion

The magnitude of side effects of ritodrine is not small. Now, it has been accepted that the so-called short-term tocolysis is considered to be the center of the strategy for the management of preterm labor. After cessation of tocolysis for 48 h, the condition of uterine contraction and cervical status should be re-evaluated. Physicians should adequately advise the patients of the risks and benefits of this drug, limit the use of this drug to the minimum, and avoid chronical administration over a long-term period.

On the other hand, it has been paid attention to the prognosis of late preterm infants from the standpoint of Developmental Origin Health and Disease (DOHaD) [30]. In addition, recent data indicate that betamethasone decreases newborn respiratory morbidity when given to women in the late preterm period between 34 0/7 weeks and 36 6/7 weeks who are at risk of preterm delivery within 7 days and who have not received corticosteroids [31]. If benefit can be also demonstrated in the other studies, consideration may be given to use of tocolysis to delay delivery to permit administration of antenatal corticosteroids through 36 weeks' gestation [24].

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Prevention and Tocolytic Agents 2

11

Masanao Ohashi

Abstract

Preterm birth is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. Preterm infants are particularly vulnerable to complications with the increasing contribution of neonatal deaths to overall child mortality. Infant mortality and morbidity from preterm birth can be reduced through interventions given to the mother before or during pregnancy, and to the preterm infant after birth. The most beneficial interventions are those that aim to improve outcomes for preterm infants when preterm birth is inevitable. Magnesium sulfate ($MgSO_4$), one of the most commonly used tocolytic agents, has been used in obstetrics for decades, and thousands of women have been enrolled in clinical trials to study the efficacy of prenatal $MgSO_4$ for a variety of conditions including recent studies that demonstrated neuroprotective effects in infants with eclampsia. The uses of $MgSO_4$ in the context of appropriate clinical obstetric practice include fetal neuroprotection before anticipated early preterm (<32 weeks of gestation) delivery. $MgSO_4$ also may be used to prolong the pregnancy to allow for the administration of antenatal corticosteroids between 24 and 34 weeks of gestation.

Keyword

Long-term tocolysis · Preterm delivery · Magnesium sulfate · Neuroprotection

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11.1 Introduction

Preterm birth is a major cause of neonatal death and is associated with several short- and long-term infant morbidities. Tocolytics, which act to inhibit uterine contractions, are commonly used to prevent or delay preterm birth [1]. $MgSO_4$ is one of the most commonly used tocolytics. We herein discuss the use of $MgSO_4$ in the management of premature labor and its neuroprotective effects [2].

11.2 Mechanism of Action

11.2.1 Biological Properties

Magnesium is the fourth most abundant ion in the human body and contributes to several physiological processes, including storage, metabolism, and energy utilization. Magnesium ion is indispensable for DNA, RNA, and protein synthesis. It contributes to glycolysis and adenosine triphosphate (ATP) production and functions as a cell membrane stabilizer. It also plays important roles in the cardiac function, muscle contraction, vascular tone, nerve impulses through its physiological role as a calcium channel blocker [3], and the regulation of sodium and potassium flow through its action on ion pumps, for example, Na+/K+ ATPase and other membrane receptors, including nicotinic acetylcholine receptors [4]. In the brain, magnesium is mainly bound to chelating agents, such as ATP, and is a cofactor in more than 300 enzymatic reactions [5]. In the central nervous system, magnesium is a noncompetitive blocker of N-methyl-aspartate (NMDA) glutamate receptor and regulates calcium influx [3]. Sixty percent of magnesium is stored in the bone, 20% in muscle, and 20% in soft tissue. Magnesium is mainly present in an ionized state (60%) but may form complexes with proteins (33%) or anions (7%). The normal plasma magnesium concentration is 0.45–1.05 mmol/L in adults [6], while that in the first week of life in newborns is 0.55–1.26 mmol/L [7].

11.2.2 Uterine Contraction

The mechanism of magnesium's effects on uterine contraction has not been completely elucidated despite more than 40 years of studies on the topic. At the level of voltage-gated channels on plasma membranes, magnesium probably competes with calcium. It hyperpolarizes the plasma membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium at this site. The inhibition of myosin light-chain kinase activity reduces myometrial contractility [8–10].

11.2.3 Neuroprotection

Magnesium has several biological effects that may contribute to protecting the preterm neonatal brain [11]; however, the precise mechanism underlying its neuroprotective effects is unknown. The most common pathological lesion associated with

cerebral palsy in preterm infants is periventricular white matter injury [12]. Oligodendrocytes constitute the major glial population in white matter. NMDA receptors on oligodendrocytes play an important role in the glial injury process. NMDA receptor antagonists have been shown to be potent neuroprotective agents in numerous animal models of perinatal brain injury. $MgSO_4$ acts as a calcium antagonist reducing calcium influx into cells [13, 14], which may reverse the adverse effects of hypoxia/ischemic brain injury by blocking NMDA receptors. $MgSO_4$ is also involved in the protection of tissue against free radical activity [13], acts as a vasodilator [15], reduces vascular instability, prevents hypoxic injury, attenuates cytokine or excitatory amino acid-induced cytotoxicity [16], and has anti-apoptotic actions [17].

11.3 Preclinical Study

Since the 1980s, animal experiments have studied the neuroprotective effects of magnesium. The initial studies included adult animal models of hypoxia, stroke, and traumatic brain injury [18]. In 1989, McIntosh et al. demonstrated that the post-traumatic injection of $MgSO_4$ reduced neurological disorders in a dose-dependent manner in a rat brain injury model [19].

In 1996, Marinov et al. proved that the neuroprotective effect of intraarterial $MgSO_4$ in rats with reversible focal ischemia was dose-dependent and related to the duration of ischemia by blocking the NMDA receptor [20]. The neuroprotective effects of $MgSO_4$ on the developing brain have been examined in several animal models. The importance of the timing of $MgSO_4$ administration has been reported. The intraperitoneal administration of $MgSO_4$ was shown to reduce the excitotoxic brain lesions in mice induced by the intracerebral injection of ibotenate (a glutamate receptor agonist) until postnatal day (P)5—which was comparable to brain lesions in humans at 32 weeks of gestation (WG) [21]. In this P5 (32 WG) model, $MgSO_4$ prevented movement disorder, fine motor skill change, and memory impairment in adolescent mice [22]. With the Rice–Vannucci procedure (surgical ligation of the right carotid artery followed by exposure to 8% oxygen for 1–2 h) of focal hypoxic-ischemic encephalopathy in the rat, $MgSO_4$ injection prior to the hypoxic episode on P7 resulted in the reduction of lesion size, hippocampal apoptosis, and the improvement of adult sensorimotor performance [17, 23]. In this model, $MgSO_4$ preserved mitochondrial respiration and reduced inflammation, thus decreasing the production of reactive oxygen species after hypoxic ischemia [24]. Our group has also reported the effect of magnesium during perinatal period for the past 20 years. First, we used chronically catheterized goat fetuses that were directly infused with either magnesium or normal saline for 4 h. The infusion of $MgSO_4$ significantly decreased the baseline fetal heart rate (FHR), short-term variability, long-term variability, and reactivity in the FHR patterns of goats at 0.85 gestation [25]. The FHR was significantly decreased by hypoxemia with increase in variability in controls. In the magnesium group, the FHR was not significantly decreased by hypoxemia. Acute hypoxemia also increased the FHR variability during magnesium infusion, which was significantly reduced in comparison to that in the control population

[26]. Second, in the P7 rat, the long-term administration of $MgSO_4$, which lasted for three consecutive days, inhibited caspase-3 activation and MAP-2 immunostaining, and resulted in significantly decreased cyst formation from necrosis, and significantly decreased neuronal loss in the cerebral cortex and the hippocampus. These results suggested that magnesium inhibited apoptotic neuronal death of hypoxia-ischemia and the neuroprotective effects against hypoxia-ischemia [27, 28]. The neuroprotective effect of $MgSO_4$ was also assessed under inflammatory conditions using a mouse model in which preterm birth mouse was induced by the administration of lipopolysaccharide and showed that $MgSO_4$ ameliorated neuronal injury in inflammation-associated preterm birth, which may have a preventive effect against cerebral palsy [29].

11.4 Clinical Effects in Pregnancy

11.4.1 Tocolytic Agents

For several decades, $MgSO_4$ has been used in obstetrics as a tocolytic agent and for the prevention or treatment of eclampsia [30, 31]. Contrary to the strong evidence indicating its effectiveness in preventing eclampsia, $MgSO_4$ is ineffective in treating preterm birth. In 2014, in a systematic review of randomized studies comparing $MgSO_4$-treated non-treated/placebo-controlled groups, Crowther et al. reported that the administration of $MgSO_4$ was associated with a significant reduction of births within 48 h of study initiation (RR, 0.56, 95% CI, 0.27–1.14; targeted at 182 women), with no improvement in the neonatal or maternal outcomes. The efficacy of $MgSO_4$ was not significantly different from that of other tocolytic agents (beta mimetic, calcium antagonist, Cox inhibitor, prostaglandin inhibitor, human chorionic gonadotropin) in 33 comparative trials [32]. The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine regard $MgSO_4$ as an option for the short-term prolongation of pregnancy (up to 48 h) and recommended the administration of antenatal corticosteroids to pregnant women at risk for preterm delivery within 7 days [33]. According to a systematic review of randomized trials, after the acute prevention of preterm labor, maintenance tocolysis with $MgSO_4$ did not prolong pregnancy, prevent preterm birth, or improve neonatal outcomes in comparison to placebo/non-treatment [34].

11.4.2 Neuroprotective Effects

In the late 1990s, some observational studies discussed the effects of $MgSO_4$ on neurological outcomes in preterm infants. Nelson and Gather reported that exposure to $MgSO_4$ was higher in the control group than in a group of children with cerebral palsy (odds ratio [OR], 0.14; 95%CI, 0.05–0.51) [35]. A meta-analysis of these

observational studies focused on the finding that antenatal $MgSO_4$ treatment was associated with a significantly reduced risk of mortality (risk ratio [RR], 0.73; 95% CI, 0.61–0.89) and cerebral palsy (OR, 0.64; 95% CI, 0.47–0.89) [36]. Antenatal $MgSO_4$ treatment was also associated with a decreased incidence of apparent echodensity and echolucency on neonatal cranial ultrasonography and cerebellar hemorrhage on MRI [37, 38].

11.4.2.1 Randomized Controlled Trials (RCTs)

There have been three major trials designed solely to assess the neuroprotective benefits of $MgSO_4$ with significant heterogeneity: the Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO_4) [39], the Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trial [40], and the PREMAG trial [41]. These trials are summarized in Table 11.1. As cerebral palsy and death are competing outcomes, it is important to use the combined outcome of "cerebral palsy or death."

Table 11.1 RCTs to assess the neuroprotective effect of $MgSO_4$

Trial	Number of subjects	GW at randomization	$MgSO_4$ dose	Death	Cerebral palsy	Composite outcome
ACTOMgSO_4	1062	<30	4 g loading dose followed by 1 g/h for maximum of 24 h	13.8 vs 17.1% RR 0.83 [0.64–1.09]	6.8 vs 8.2% RR 0.83 [0.54–1.27]	Death or cerebral palsy: 19.8 vs 24.0% RR 0.83 [0.66–1.03]
BEAM	2241	24–31	6 g loading dose followed by 2 g/h for maximum of 12 h	9.5 vs 8.5% RR 1.12 [0.85–1.47]	Moderate to severe cerebral palsy: 1.9 vs 3.5% RR 0.55 [0.32–0.95[a]]	Stillbirth, infant death by 1 year, moderate to severe cerebral palsy >2 years of corrected age: 11.3 versus 11.7% RR 0.97 [0.77–1.23]
PREMAG	573	<33	4 g loading dose No maintenance dose			Death or cerebral palsy: OR 0.65 [0.42–1.03] Severe motor dysfunction or death: OR 0.62 [0.41–0.93]

GW gestational week, *RR* relative risk, *OR* odds ratio

[a]Only infants of pregnancies randomized at <28 weeks had a significant reduction in moderate or severe cerebral palsy

Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO$_4$)
A total of 1062 women in preterm labor before 30 WG from 16 centers were included in the Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO$_4$) between February 1996 and September 2000. MgSO$_4$ (4 g loading followed by 1 g/h maintenance for 24 h or until birth) was randomly allocated to 535 women (629 live fetuses), while 527 women (626 live fetuses) received placebo. The primary study outcome, which was the rate of cerebral palsy, indicated no significant difference between the two groups (6.8% in the MgSO$_4$ group versus 8.2% in the control group; RR, 0.83; 95% CI, 0.54–1.27); however, the rate of motor dysfunction was significantly lower in the MgSO$_4$ group (3.4 versus 6.6% in the control group; RR, 0.51; 95% CI, 0.29–0.91).

The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM)
The BEAM trial included 2241 women with preterm labor before 32 WG who were managed at 20 facilities between December 1997 and May 2004. They were randomized to receive a 6 g bolus of MgSO$_4$ followed by a 2 g/h maintenance dose for 12 h (1096 women, 1188 fetuses) or placebo (1145 women, 1256 fetuses). The rates of pediatric mortality did not differ between the two groups to a statistically significant extent. Although the primary outcomes (composite of stillbirth or death by 1 year or cerebral palsy at 2 years) were similar in the two groups, the incidence of moderate or severe cerebral palsy was significantly reduced in the MgSO$_4$ group (1.9 versus 3.5%; RR, 0.55; 95% CI, 0.32–0.95).

PREMAG Trial
The PREMAG trial included 564 women treated at 18 French centers between July 1997 and July 2003, with 286 women (354 fetuses) randomly assigned to receive a 4 g bolus of MgSO$_4$ and 278 women (341 fetuses) who were randomly assigned to receive placebo. The trial was discontinued after 6 years of enrollment. The primary outcomes (the rates of white matter injury and mortality) were similar between the groups (white matter injury, 10.0% versus 11.7%; OR, 0.78; 95% CI, 0.47–1.31; mortality, 9.4 versus 10.4%; OR, 0.79; 95% CI, 0.44–1.44). The rate of combined death or gross motor dysfunction at 2 years was lower in the MgSO$_4$ group (25.6 versus 30.8%; OR, 0.62; 95% CI, 0.41–0.93), but there was no difference in the incidence of cerebral palsy [42].

11.4.2.2 Meta-Analyses

Five RCTs [12, 43–46] have been the focus of four meta-analyses with consistent findings and conclusions (Table 11.2). In all meta-analyses, the antenatal administration of MgSO$_4$ to women at risk of preterm delivery was associated with a significantly reduced risk of cerebral palsy in children exposed in utero, with an RR ranging from 0.61 to 0.70 and no effect on mortality. The number of women needed to treat (NNT) to avoid one case of cerebral palsy ranged from 46 to 74 in infants born before 34 WG. Mild maternal side effects (e.g., flushing, nausea or vomiting, sweating, injection site discomfort) were more frequent in the MgSO$_4$ groups, but there were no significant severe side effects. Furthermore, an individual participant

Table 11.2 Main outcomes of the meta-analyses

Authors	Published year	Pediatric mortality[a]	Cerebral palsy[a]	Death or cerebral palsy[a]	NNT to avoid one cerebral palsy[b]
Doyle et al. [44]	2009	1.04 [0.92–1.17]	0.68 [0.54–0.87]	0.94 [0.78–1.12]	63 [43–115]
Conde-Agudelo and Romero [12]	2009	1.01 [0.89–1.14]	0.69 [0.55–0.88]	1.01 [0.89–1.14]	74 [41–373]
Costantine and Weiner [45]	2009	1.01 [0.89–1.14]	0.70 [0.55–0.89]	0.92 [0.83–1.03]	<30WG: 46 [26–187] 32–34 WG: 56 [34–164]
Zeng et al. [46]	2016	0.92 [0.77–1.11]	Moderate to severe: 0.61 [0.42–0.89]	N/A	N/A
Crowther et al. [47] (individual participant data analysis)	2017	1.03 [0.91–1.17]	0.68 [0.54–0.87]	0.86 [0.75–0.99]	46 [not shown]

NNT number needed to treat
[a]Relative risk [95% confidence interval]
[b]Number [95% confidence interval]

data meta-analysis was undertaken by the AMICABLE group (Antenatal Magnesium sulfate Individual participant data international Collaboration: Assessing the benefits for babies using the Best Level of Evidence) to explore the interaction between treatment and participant characteristics (Table 11.2), which included the five RCTs (5493 women and 6131 babies). The overall RR for cerebral palsy among survivors after the antenatal administration $MgSO_4$ was 0.68 (95% CI, 0.54–0.87), and the NNT was 46. Interestingly, $MgSO_4$ also reduced the combined risk of fetal, infant death, and cerebral palsy in the analysis of the four trials with fetal neuroprotective intent (RR 0.86, 95% CI, 0.75–0.99) [47]. In all RCTs and meta-analyses to date, $MgSO_4$ treatment did not affect pediatric mortality or neonatal morbidity (respiratory distress syndrome, chronic lung disease, any intraventricular hemorrhage, cystic periventricular leukomalacia, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity). Similarly, $MgSO_4$ treatment was not associated with serious maternal side effects. The benefit remained constant regardless of gestational age, cause of prematurity, total dose received, and the maintenance dose administered after the loading dose.

11.5 Clinical Approach and Long-Term Tocolysis

Women at high risk of imminent preterm birth are appropriate candidates for $MgSO_4$ for protection from brain damage. None of the randomized trials of $MgSO_4$ for neuroprotection included pregnancies at <24 WG. The upper limit of gestational age for the neuroprotective effect of antenatally administered magnesium has not been well-studied [45]. In 2018, the American College of Obstetricians and

Gynecologists and the Society for Maternal-Fetal Medicine commented that they continue to support the short-term (usually <48 h) use of $MgSO_4$ in obstetric care for appropriate conditions and for appropriate durations of treatment, which includes the prevention and treatment of seizures in women with preeclampsia or eclampsia, fetal neuroprotection before anticipated early preterm (<32 WG) delivery, and short-term prolongation of pregnancy (up to 48 h) to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within 7 days [33]. The intrapartum administration of $MgSO_4$ to women with growth-restricted fetuses born at <29 weeks' gestation was associated with reduced odds of composite of death or significant neurodevelopmental impairment (adjusted OR, 0.42; 95% CI, 0.22–0.80) [48]. We favor the administration of a 4 g loading dose of $MgSO_4$ for 30 min and a maintenance dose of 1 g/h. Our group has already reported that among infants born between 28 and 32 WG survivors in the low-dose group (total $MgSO_4$ administration <50 g) had significantly reduced rates of cerebral palsy (OR 0.4, 95% CI, 0.2–0.98) and brain damage (OR 0.2, 95% CI, 0.1–0.9) [49].

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Maintenance Tocolytic Therapy

12

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Abstract

Several drugs have been developed to reduce the likelihood of preterm delivery even though its efficacy lasts <48 h. Each tocolytic agent has side effects and evidence of limited efficacy, therefore is not suitable for long-term usage. Maintenance therapy with nifedipine, ritodrine, terbutaline, or magnesium sulfate has been assessed, resulting in neither improved perinatal outcome nor pregnancy prolongation. It is conceivable that it may be beneficial to use maintenance therapy in selected cases of very preterm birth, where fetal compromise and intrauterine infection have been ruled out.

Keywords

Preterm delivery · Maintenance tocolytic therapy · Prolongation pregnancy Perinatal outcome

12.1 Introduction

Preterm birth is the leading cause of neonatal mortality and morbidity in developed countries. In this regard, several drugs have been developed to reduce the likelihood of preterm delivery <48 h, although effectiveness beyond this period has not been established. Short-term prolongation of pregnancy (<48 h) allows the complete a course of antenatal corticosteroids and magnesium sulfate for neuroprotection, as well as maternal transfer to a tertiary facility, which are very beneficial both to fetus and mother. After acute inhibition of preterm labor, maintenance tocolytic therapy

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has been conducted with nifedipine, terbutaline, or magnesium sulfate and assessed in systematic reviews of randomized trials [1–4].

12.2 Magnesium Sulfate

One Cochrane review which was updated in 2013 included four randomized controlled trials involving a total of 422 women [1]. In this review, the trials did not show any differences between magnesium maintenance therapy and placebo or other treatments (ritodrine or terbutaline) in the reduction of preterm birth or perinatal deaths. Magnesium sulfate has fewer side effects compared to betamimetics such as particularly palpitations or tachycardia, although diarrhea is more common. These trials were too small to exclude either essential benefits or harms, whereas none of them looked at the infant's long-term development. In 2013, Food and Drug Administration (FDA) had warned against long-term use of magnesium sulfate exposed for more than 5–7 days, which may lead to low calcium levels and bone problems in the developing baby or fetus, including osteopenia and fractures [5]. The shortest duration of treatment that can result in harm to the baby is also not known. Based on these findings, it is inappropriate to use magnesium sulfate beyond 48 h as a tocolytic agent, and it should use if needed clearly.

12.3 Betamimetics

Of betamimetics, terbutaline is commonly used in the USA, whereas ritodrine is commercially available and still used in Japan as a tocolytic agent. Conversely, ritodrine was withdrawn from the US market in 2003. In randomized studies, intravenous ritodrine has been shown to delay the delivery from 24 to up to 48 h [6]. Long-term usage of ritodrine for tocolysis will not be authorized in the standpoint of its multiple adverse effects unless close monitoring is paid to both fetus and mother in the case of unavoidable circumstances.

Terbutaline is taken orally, though, it does not seem to prevent returning contractions. In Cochrane review, oral betamimetics for maintenance therapy after threatened preterm labor do not reduce the incidence of preterm labor, based on 13 randomized controlled trials with a total of 1551 women [2]. The betamimetics ritodrine and terbutaline did not reduce the rate of preterm birth or prevent problems with neonates that required admission to the neonatal intensive care unit when compared with placebo, no treatment, or other tocolytic drugs. Another option of terbutaline is to use a small portable pump that feeds a continuous dose under the skin. Such low-dose terbutaline maintenance therapy with subcutaneous pump can be administered long term, which has been evaluated by a Cochrane review last updated in 2014 [3]. They found no evidence that terbutaline pump maintenance therapy decreased adverse neonatal outcomes. In 2011, the Food and Drug Administration (FDA) issued warnings specifically cautioning against the use of maintenance oral terbutaline during pregnancy because of reports of serious side effects [7]. Physicians

should be aware that death and serious adverse reactions could occur, including increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. These side effects were usually confirmed after prolonged administration both in oral or subcutaneous use. American College of Obstetrics and Gynecology (ACOG) recommends only short-term usage as a tocolytic or as acute therapy of uterine tachysystole with subcutaneous dosages of 0.25 mg [8]. Of note, oral terbutaline is ineffective to treat preterm labor and if injectable terbutaline is needed, it should not be used in the outpatient or home setting. The FDA recommends treatment with terbutaline administered by injection or by continuous infusion pump has to be used no longer than 48–72 h [7].

In Japan, it is commonly used ritodrine and/or magnesium sulfate as long-term tocolytic agents. Thus we performed a retrospective study to determine the efficacy of long-term tocolytic therapy (for more than 4 days) [8]. Between 1998 and 2005, 48 singleton pregnant women with uncomplicated preterm labor and intact membranes were enrolled. They are treated with long-term tocolytic therapy with intravenous magnesium sulfate and/or ritodrine for more than 4 days until 35 weeks of gestation (tocolysis off group). Controls were uncomplicated singleton pregnancies ($n = 419$) and enrolled at 35 weeks gestation. We determined the incidence of preterm delivery after cessation of agents, which was compared with the controls. Preterm birth occurred significantly more often in tocolysis off group compared with controls (58% versus 4%, $P < 0.01$). The odds ratio of preterm birth was 40 (95% confidence intervals: 16–98). These results suggest that long-term tocolysis is beneficial to prolong pregnancy in at least 58% of treated patients.

We evaluated the efficacy of magnesium sulfate as a second-line tocolysis for 48 h [9]. A multi-institutional, simple 2-arm randomized controlled trial was performed. Forty-five women at 22–34 weeks of gestation were eligible, whose ritodrine did not sufficiently inhibit uterine contractions. After excluding 12 women who failed to meet the inclusion criteria of preterm labor, 33 were randomly assigned to either magnesium alone or combination of ritodrine and magnesium. The treatment was determined as effective if the frequency of uterine contraction was reduced by 30% at 48 h of the treatment. After magnesium sulfate infusion, 90% prolonged their pregnancy for >48 h. Combination therapy was effective in 95% (18/19), which was significantly higher than 50% (7/14) for magnesium alone. Our randomized trial revealed that combination therapy significantly reduced uterine contractions, suggesting that adjuvant magnesium with ritodrine is recommended, rather than changing into magnesium alone, when uterine contractions are intractable with ritodrine alone.

12.4 Oxytocin Receptor Antagonists

The only tocolytic that has been shown to prolong gestation as maintenance therapy is oxytocin receptor antagonists, atosiban [10]. Atosiban is not available in the USA and also in Japan. Romero and coworkers reported that treatment for preterm labor with atosiban resulted in prolongation of pregnancy for up to 7 days for those at a gestational age at or more than 28 weeks, occurring with less maternal-fetal adverse

effects [10]. While in a Cochrane review of oxytocin receptor antagonists (largely atosiban) as a tocolytic agent did not demonstrate the superiority of oxytocin receptor antagonists compared with placebo, betamimetics, or calcium channel blocker (largely nifedipine) [11]. Concern to maintenance therapy with atosiban, Valenzuela and colleagues performed a multicenter, double-blind, placebo-controlled trial [12] which was also reviewed in Cochrane review [13]. This trial compared atosiban with placebo, both administered by a subcutaneous infusion pump to women in whom preterm labor had ceased following treatment with atosiban. In both groups, atosiban or matching placebo was given as subcutaneous infusion continuously. Atosiban infused of 6 mL/h (30 μg/min) to the end of 36 weeks' gestation. Compared with placebo, the use of atosiban as maintenance therapy for prevention of recurrent preterm labor did not reduce the incidence of preterm birth. While the median interval from the start of maintenance therapy to the first recurrence of labor was prolonged (32.6 days versus 27.6 days), as was the time to recurrence of preterm labor (36.2 versus 28.2 days).

12.5 Calcium-Channel Blockers

Calcium-channel blockers, especially nifedipine is safer and more effective as a tocolytic agent than betamimetics, but only sometimes more effective than other types of tocolytics [14]. However, maintenance therapy with nifedipine does not show a reduction in preterm birth or improvement in neonatal outcomes. van Vliet and colleagues performed a meta-analysis, compared maintenance nifedipine tocolysis with placebo or no treatment [4]. Six randomized controlled trials were enrolled, encompassing data from 787 patients. There was no difference between these two groups for the incidence of perinatal death, neonatal mobility, and prolongation of pregnancy.

12.6 Conclusions

Tocolytic agents are usually used up to 48 h to prolong pregnancy to afford time for maternal transfer, infusion of magnesium sulfate for neuroprotection, and fetal maturation after administration of an antenatal corticosteroid. After the acute inhibition of preterm labor, maintenance therapy with tocolytic agents is not recommended. Because systematic reviews of randomized trials have consistently found ineffective evidence in both for preventing preterm birth and improving neonatal outcome. Additionally, maintenance therapy just for pregnancy prolonging could be harmful both to the mother and the fetus due to their severe adverse effects. It is conceivable that it might be beneficial to use maintenance therapy in selected cases of very preterm birth, at least where fetal compromise intrauterine infection has been ruled out and in the unavoidable circumstances.

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Antibiotics for Preterm Labor

13

Yohei Maki

Abstract

Since intrauterine infection is the most frequent cause of preterm birth, numerous trials have been attempted on the antibiotic treatment of various conditions. There is insufficient evidence to recommend treatment of genital tract infection in early pregnancy to reduce the prevalence of preterm birth. Routine antibiotics in pregnant women with preterm labor and intact membranes can have harmful effects on the neonatal outcome. Thus, antibiotic administration should be withheld unless obvious infection signs are observed. The efficacy of antibiotic administration has been established in prelabor premature rupture of membranes. However, clinicians should be cautious regarding the development of resistant organisms after prophylactic antibiotics. Once a pregnant woman is diagnosed with or suspected to have intrauterine infection, immediate initiation of antibiotic therapy is recommended. Since intrauterine infection is usually polymicrobial involving both aerobic and anaerobic bacteria, antibiotics should cover these microorganisms. The optimal antibiotic regimen has not been well-studied. Amniotic fluid sample obtained by transabdominal amniocentesis in pregnant women with suspected intrauterine infection can determine antibiotic susceptibility and the efficacy of an antibiotic treatment. Expectant management with antibiotic treatment may contribute to prolongation of pregnancy duration; however, strict observation of the fetal condition is necessary.

Keywords

Chorioamnionitis · Preterm birth · Antibiotics · Prelabor premature rupture of membranes

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13.1 Antibiotics for the Prevention of Preterm Birth

Maternal genital tract colonization with various pathogens including Ureaplasma species [1, 2], *Chlamydia trachomatis* [3–6], and *Trichomonas vaginalis* [4, 7] can be associated with preterm birth. Antibiotic treatment against these pathogens during pregnancy has been attempted to prevent preterm birth.

Erythromycin treatment in pregnant women with vaginal Ureaplasma species colonization in the third trimester decreased the prevalence of low-birth-weight infants in a randomized double-blind study [8]. However, a large, randomized, double-blind, multicenter clinical trial showed that erythromycin treatment for pregnant women with *Ureaplasma urealyticum* colonization in the vagina between 26 and 30 weeks of gestation did not prevent preterm birth [9]. The Cochrane Review including one trial and 1071 patients concluded that the evidence was insufficient to assess whether Ureaplasma colonization in the genital tract should be treated to prevent preterm birth [10].

A double-blind, randomized, placebo-controlled trial showed that treatment of a chlamydia infection during pregnancy had little effect on reducing preterm delivery [11]. However, a systematic review and meta-analysis including 24 studies revealed that pregnant women with chlamydia infection had a significantly higher prevalence of preterm delivery with an odds ratio (OR) of 2.28 [95% confidence interval (CI), 1.64–3.16] [12], although some recent studies resulted in negative [13, 14].

Interestingly, metronidazole treatment for asymptomatic Trichomonas infection at 24–29 weeks of gestation increased the risk of preterm delivery with a relative risk (RR) of 3.0 (95% CI, 1.5–5.9) [15]. The authors hypothesized that a dying Trichomonas caused an inflammatory response, resulting in preterm labor.

Additionally, whether vaginal candidiasis treatment reduces the prevalence of preterm birth remains controversial. A systematic review and meta-analysis using two studies and 685 patients showed that treatment of asymptomatic candidiasis may reduce the risk of preterm birth, although the evidence was insufficient because the result included unplanned subgroup analysis [16].

Treatment of bacterial vaginosis is discussed in Chap. 18.

There are some trials on the antibiotic treatment of pregnant women with a specific condition. A randomized clinical trial showed that metronidazole plus erythromycin for pregnant women with a positive fetal fibronectin between 21 and 25 weeks of gestation did not reduce the risk of preterm delivery [17]. Moreover, another randomized controlled trial revealed that metronidazole for pregnant women with a positive fibronectin and a risk of preterm birth, including mid-trimester loss or preterm delivery, uterine abnormality, cervical surgery, or cerclage, between 24 and 27 weeks of gestation did not reduce the prevalence of preterm birth [18].

Pregnant women with amniotic fluid sludge detected by ultrasonography are potential candidates for antibiotic prophylaxis. A historically controlled observational study has shown that antibiotic treatment reduced the prevalence of preterm birth at <34 weeks in women at high risk for preterm birth (i.e., cervical length ≤25 mm, history of spontaneous preterm birth, previous spontaneous loss in the

second trimester, uterine malformations, or cervical conization) with an OR of 0.24 (95% CI, 0.06–0.99) [19], although its evidence level is low. Hence, further research is needed.

Overall, the Cochrane Review including eight trials and approximately 4300 patients reviewed the effect of prophylactic antibiotic treatment for women in the second or third trimester and concluded that antibiotic prophylaxis during pregnancy did not reduce the risk of preterm prelabor rupture of membranes (relative ratio (RR), 0.31; 95% CI, 0.06–1.49) or preterm delivery (RR, 0.88; 95% CI, 0.72–1.09) [20].

In conclusion, there is an insufficient evidence to recommend treatment of genital tract infection to reduce the prevalence of preterm birth. However, the use of antibiotic treatment to prevent the spread of sexual transmitted infection or for symptomatic patients is justified.

13.2 Antibiotics for Preterm Labor with Intact Membranes Without Evidence of Infection

Some clinicians favor the use of antibiotics in pregnant women with preterm labor because intrauterine infection is an important cause of preterm labor. However, routine prophylactic antibiotics should be avoided in those with preterm labor and intact membranes.

The ORACLE II study is the largest trial involving 6295 patients which compared erythromycin (n = 1611), co-amoxiclav (amoxicillin and clavulanic acid; n = 1550), both (n = 1565), or placebo (n = 1569) for 10 days or until delivery among pregnant women with preterm labor and intact membranes, but without any signs of clinical infection. This study failed to demonstrate the benefits of antibiotic use for the reduction of neonatal composite outcome including neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography [21].

Furthermore, the Cochrane Review reviewed 14 studies and concluded that the use of prophylactic antibiotics in pregnant women with preterm labor and intact membranes had no beneficial effects on the neonatal outcome. It is important to note that the incidence of neonatal death increased in women who received prophylactic antibiotics compared to those without antibiotics (RR, 1.57; 95% CI, 1.03–2.40). In a subgroup analysis, cerebral palsy significantly increased in infants born to women with combined macrolide and beta-lactam antibiotics compared to those receiving placebo (RR, 2.83; 95% CI, 1.02–7.88). The prevalence of neonatal death (RR, 1.52; 95% CI, 1.05–2.19), any functional impairment (RR, 1.11; 95% CI, 1.01–1.20), and cerebral palsy (RR, 1.90; 95% CI, 1.20–3.01) increased in infants whose mothers received any macrolide antibiotics compared to those who received no macrolide antibiotics (including placebo and co-amoxiclav alone) [22].

These findings suggest that routine antibiotics should be withheld in pregnant women with preterm labor and intact membranes, unless obvious infection signs are manifested.

13.3 Antibiotics for Prelabor Premature Rupture of Membranes (pPROM) Without any Sign of Infection

In contrast to preterm labor with intact membranes, the efficacy of antibiotic administration has been established in pPROM.

The first large randomized controlled trial conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network in 1997 demonstrated the impact of antibiotic prophylaxis on pPROM management [23]. A total of 614 pregnant women with pPROM between 24 and 32 weeks of gestation were included and randomly assigned to receive intravenous ampicillin (2 g every 6 h) and erythromycin (250 mg every 6 h) for 48 h, followed by oral amoxicillin (250 mg every 8 h) and erythromycin (333 mg every 8 h) for 5 days or placebo. Group B streptococcus (GBS) carriers were identified and treated. Tocolytics and corticosteroids were withheld after randomization. The prevalence of neonatal composite adverse outcomes (i.e., fetal or infant death, respiratory distress, severe intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, or sepsis) (44.1% vs 52.9%), respiratory distress (40.5% vs 48.7%), and necrotizing enterocolitis (2.3% vs 5.8%) was significantly lower in the antibiotics group than that in the placebo group. Among the GBS negative women, the antibiotics group had a prolonged median time to delivery compared to the placebo group (6.1 days vs 2.9 days). About half of antibiotics group remained pregnant at 7 days after treatment, while about 25% of placebo group did.

The second impact trial was the ORACLE trial in 2001 [24]. This is the largest trial which included a total of 4826 pregnant women with pPROM at less than 37 weeks of gestation. They were randomly assigned to oral 250 mg erythromycin ($n = 1197$), 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid; $n = 1212$), both ($n = 1192$), or placebo ($n = 1225$) four times daily for 10 days or until delivery. The prevalence of neonatal composite adverse outcomes (i.e., neonatal death, chronic lung disease, or major cerebral abnormality) was lower in the erythromycin only group than that in the placebo group, although it was not statistically significant (12.7% vs 15.2%, $p = 0.08$). Importantly, the co-amoxiclav only group had a higher incidence of necrotizing enterocolitis than the placebo group (1.9% vs 0.5%). Additionally, the any co-amoxiclav group had a higher incidence of necrotizing enterocolitis than the no co-amoxiclav group (1.8% vs 0.7%). Therefore, co-amoxiclav is not recommended for pregnant women with pPROM.

The Cochrane Review included 12 studies and reported that antibiotic treatment in pregnant women with pPROM statistically significantly reduced the prevalence of chorioamnionitis (RR, 0.66; 95% CI, 0.46–0.96), prolonged the latency period for 48 h (RR, 0.71; 95% CI, 0.58–0.85) and 7 days (RR, 0.79; 95% CI, 0.71–0.89), neonatal infection (RR, 0.67; 95% CI, 0.52–0.85), surfactant use (RR, 0.83; 95% CI, 0.72–0.96), oxygen therapy (RR, 0.88; 95% CI, 0.81–0.96), and abnormal cerebral ultrasound scan (RR, 0.81; 95% CI, 0.68–0.98). Co-amoxiclav was associated with an increased risk of neonatal necrotizing enterocolitis (RR, 4.72; 95% CI, 1.57–14.23) [25].

The most optimal regimen and duration of antibiotics have yet to be established. The combination of ampicillin/amoxicillin and erythromycin following the NICHD trial is commonly used.

Clinicians should be cautious on the development of resistant organisms following the use of prophylactic antibiotics. Basically, single antibiotic and short-term is favorable. Only small studies have revealed three-day regimen had no difference in outcomes, compared with seven-day regimen [26, 27]. Hence, a larger study is necessary.

13.4 Antibiotics for Diagnosed or Suspected Intrauterine Infection

13.4.1 Timing of Antibiotic Treatment

If a pregnant woman is diagnosed with or suspected to have intrauterine infection, immediate initiation of antibiotic therapy is recommended. There is only one small randomized prospective trial involving 45 pregnant women [28] which compared intrapartum treatment and immediate postpartum treatment. The antibiotics were intravenous ampicillin 2 g every 6 h plus gentamicin 1.5 mg/kg every 8 h. In addition, patients delivered by cesarean section received clindamycin 900 mg every 8 h. The incidence of neonatal sepsis was lower (0% vs 21%) and the neonatal hospital stay was shorter (3.8 days vs 5.7 days) in the intrapartum antibiotic group than that in the postpartum antibiotic group. Similarly, the intrapartum antibiotic group had significantly shorter maternal postpartum hospital stay (4.0 days vs 5.0 days) and febrile days (0.44 days vs 1.5 days) than the postpartum antibiotic group. A retrospective study also showed that intrapartum antibiotic treatment had a lower incidence of neonatal sepsis ($p = 0.06$) [29].

13.4.2 Antibiotic Regimen

Intra-amniotic infection is usually polymicrobial involving both aerobic and anaerobic bacteria. Therefore, antibiotics should cover these microorganisms. The optimal antibiotic regimen has not been well-studied.

A combination of intravenous ampicillin and gentamicin is traditionally preferred since GBS and *Escherichia coli* are the most common pathogens of neonatal sepsis. These agents have lack of activity against anaerobic coverage. Therefore, addition of clindamycin is recommended for the treatment of women undergoing cesarean section. However, a randomized controlled study failed to demonstrate the benefit of adding clindamycin to ampicillin and gentamicin in the prevalence of endometritis, neonatal sepsis, or mortality [30]. On the other hand, the Cochrane Review reported that the combination of clindamycin and gentamicin is the most effective agent for the treatment of endometritis [31].

Gentamicin is traditionally administered in small doses every 8 h. A high dose of gentamicin given every 24 h is recently recommended. It has the advantages of possible concentration-dependent killing, post-antibiotic effect, and decreased nephrotoxicity. Several studies have been conducted on adults and children with various conditions.

Once-daily high-dose administration gives optimal fetal serum peak level that is closer to optimal neonatal values with shorter time below the toxicity threshold, suggesting a decreased risk of fetal nephrotoxicity and ototoxicity, compared with the conventional three times daily administration (Locksmith). However, there is no evidence that showed a significant difference in maternal or neonatal outcomes [32, 33].

A randomized double-blind trial comparing piperacillin to cefoxitin showed a similar effect on postpartum endometritis. This study did not evaluate the neonatal outcome [34].

Although Ureaplasma species are the most common organism in women with intrauterine infection, it is not well-known whether the maternal administration of antibiotic should cover them. The addition of macrolide or clindamycin is reasonable if genital mycoplasma is identified.

13.4.3 Duration of Antibiotic Treatment

Some studies have evaluated the optimal duration of antibiotic treatment from the standpoint of maternal postpartum outcome. Single-dose cefotetan was associated with a shorter hospital stay, with a similar incidence of failed treatment, compared with multiple-dose cefotetan in a randomized controlled trial [35]. A randomized controlled study has shown that single additional postpartum antibiotic treatment had the same effect on treatment failure, compared with those with no additional treatment. The authors concluded that if intrapartum antibiotic treatment is promptly initiated, additional postpartum treatment is unnecessary [36]. Further oral antibiotic is also not beneficial [37.]

13.4.4 Antibiotic Treatment for Confirmed Intra-Amniotic Infection

Whether antepartum antibiotic treatment in women with preterm labor or pPROM can eradicate the microorganism is not well-understood. Obtaining the amniotic fluid by transabdominal amniocentesis in pregnant women with suspected intrauterine infection for the identification of microorganisms can determine antibiotic susceptibility and the efficacy of an antibiotic treatment.

One study has shown that the antibiotic treatment for pregnant women with pPROM and confirmed intra-amniotic infection failed to eradicate the microorganisms. Among the seven pregnant women with a positive amniotic fluid culture at admission, six of them still had a positive amniotic fluid culture after 10–14 days of antibiotic treatment. Moreover, intra-amniotic inflammation developed in one-third

of women without intra-amniotic infection and inflammation at admission despite antibiotic treatment [37]. A recent study has shown that among 50 pregnant women with preterm labor and intact membranes who had a confirmed intra-amniotic infection/inflammation, only 16 of them (32%) had a successful eradication of microorganisms (15/50) or delivery after 37 weeks of gestation (1/50). Interestingly, 29 of 50 women (58%) were still pregnant for more than 7 days. The median amniocentesis-to-delivery interval was significantly longer among women who received a combination of antibiotics than those who did not receive such treatment (11 days vs 3 days) [38]. Expectant management with antibiotic administration under strict observation of the fetal well-being may be an option to prolong the pregnancy duration.

Identification of microorganisms by amniotic fluid culture obtained through transabdominal amniocentesis may be necessary for choosing the appropriate antibiotic which may prolong the pregnancy [39]. However, its effect on the neonatal outcome is not established. Careful fetal monitoring is required for the prolongation of pregnancy with antibiotic treatment. Clinicians should consider the risk of prematurity and severity of fetal infection/inflammation.

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Probiotics for Preterm Labor

14

Masato Kamitomo

Abstract

Preterm labor may be induced by infection pathways, including ascending infection, hematogenous transplacental infection, and transovarial disseminated infection. Causative bacteria may originate from the vagina, intestinal tract, or oral cavity; however, approximately 90% of cases involve an ascending infection from the vagina, and the presence of abnormal microbiota in the vagina is a major cause of preterm labor. Conversely, in recent years, researchers have alluded that abnormal microbiota in the gut causes a pro-inflammatory state, which could contribute to preterm labor. The administration of probiotics to improve this state and thereby prevent preterm labor is being studied; however, at this time, although probiotics can normalize vaginal microbiota, there is no clear evidence that they can prevent preterm labor. To clarify the therapeutic effects of probiotics in preventing preterm labor, a randomized controlled trial is required, wherein the type of bacteria administered, starting time, administration duration, and treatment subjects are taken into account.

Keywords

Preterm labor · Probiotics · Gut microbiota

14.1 Introduction

The main difference between preterm labor and full-term labor is the time when the mechanism of labor commences, whereas the physiological process leading to delivery is the same (i.e., the process involving increased contractile activity

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of the uterine smooth muscle, ripening of the cervical canal, and rupture of the fetal membrane). Up to a certain time, regardless of whether the uterine muscle is active or at rest, once the mechanism of labor begins, the intrauterine environment changes from an anti-inflammatory state to a pro-inflammatory state; the cervical canal starts to ripen, which triggers active labor, thereby intensifying the contractile activity of uterine muscles, which in turn leads to delivery. Substances that cause these changes include chemokines (interleukin-8), cytokines (interleukin-1 and -6), and uterine contraction-related proteins (oxytocin receptor, connexin 43, and prostaglandin receptors), which play a key role in the mechanism of labor [1]. Progesterone secreted from the placenta acts on immune cells, and the inhibition of secretion of these substances maintains the state of uterine rest [2].

In general, preterm labor tends to be regarded as a single condition; however, at present, it is understood to be a syndrome that develops with the involvement of several factors in a complicated manner (Table 14.1) [1]. Among these factors, to a certain extent, infection has been identified as a pathophysiological cause of preterm labor. The involvement of other factors has been inferred from observational and experimental studies, but several points remain unclear. The infection pathways of infection-induced preterm labor include ascending infection, hematogenous transplacental infection, and transovarial disseminated infection. Bacteria causing these infections are believed to originate from the vaginal, gut, and oral microbiota; however, approximately 90% of cases are those of ascending infection; thus, abnormal vaginal microbiota is a major cause of preterm labor [1].

To prevent and cure such infections, antibacterial agents and probiotics are administered, but their effects on preterm labor are inconsistent [3, 4]. Probiotics are microorganisms that confer health benefits on the human body; the term also refers to preparations and food products that contain them. The scope of probiotics as defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2014 is shown in Table 14.2 [5]. On several occasions, the effect of probiotics is observed by way of the gut microbiota consumed orally. In this paper, we outline the relationship between abnormal microbiota and preterm labor and the effect of probiotics.

Table 14.1 Causes of preterm labor (reference [1])

Infection
Vascular disorders
Decidual senescence
Uterine overdistension
Cervical disease
Breakdown of maternal-fetal tolerance
Stress
Unknown

Table 14.2 Consensus panel recommendations for the scope of probiotics

Retain the FAO/WHO definition[1] for probiotics, with a minor grammatical correction as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host;" inconsistences between the expert consultation and the FAO/WHO Guidelines[2] were clarified
Include in the framework for definition of probiotics microbial species that have been shown in properly controlled studies to confer benefits to health
Any specific claim beyond "contains probiotics" must be further substantiated
Keep live cultures, traditionally associated with fermented foods and for which there is no evidence of a health benefit, outside the probiotic framework
Keep undefined, fecal microbiota transplants outside the probiotic framework
New commensals and consortia comprising defined strains from human samples, with adequate evidence of safety and efficacy, are "probiotics"

ISAPP International Scientific Association for Probiotics and Prebiotics, *FAO* Food and Agriculture Organization of the United Nations, *WHO* World Health Organization

[1]Food and Agricultural Organization of the United Nations and World Health Organization. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. World Health Organization. http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf (2001).

[2]Food and Agricultural Organization of the United Nations and World Health Organization. Joint FAO/WHO working group report on drafting guidelines for the evaluation of probiotics in food. Food and Agricultural Organization of the United Nations. ftp://ftp.fao.org/es/esn/food/wgreport2.pdf (2002).

14.2 Vaginal Microbiota and Preterm Labor

Vaginal microbiota comprises >50 nonpathogenic microorganisms with great individual variation [6]. It has been found that the decreased diversity of the vaginal microbiota and low numbers of *Lactobacillus* are conducive to the onset of preterm labor [7]. The normal vagina is predominantly inhabited by *Lactobacillus,* which breaks down glycogen in the vaginal epithelium to produce lactic acid and H_2O_2, resulting in an acidic environment that inhibits the growth and dissemination of pathogens, which thereby protects the body from bacterial vaginosis, urinary tract infections, and sexually transmitted infections [8]. Furthermore, the growth of *Lactobacillus* inhibits the growth of other bacteria in a competitive manner [1].

In bacterial vaginosis, the vaginal microbiota is altered such that *Lactobacillus* numbers decrease and other bacteria become dominant. Therefore, it is believed that pathogens travel from the vagina to the cervical canal to infiltrate the uterus and cause chorioamnionitis. However, other reports indicate that although the use of antibacterial agents eliminates bacterial vaginosis, these agents cannot prevent preterm labor [9]. This suggests that factors other than microbiota, including host immunity, cervical canal factors, and the timing of treatment, are involved.

14.3 Oral Microbiota and Preterm Labor

More than 700 types of bacteria exist in the mouth, and it has been reported that bacteria found only in the mouth can cause infection in the uterus [10]. The infection pathway is often hematogenous, i.e., the infection results from periodontal disease [11]. Thus, oral bacteria can infiltrate the vagina through oral sex and such a cause of ascending infection cannot be ruled out. It has been alluded that pregnant women with periodontal disease have elevated levels of serum interleukin-8 (IL-8) and IL-1β, which could increase the incidence of preterm labor [12]; however, therapeutic intervention has not been reported to reduce preterm labor before 32 weeks of pregnancy [13]. Thus, the effects of treatment are inconsistent.

14.4 Gut Microbiota and the Intestinal Immune System

The gut contains 100–1000 trillion bacteria comprising 500–1000 bacterial species, which constitute the gut microbiota. To deal with this enormous antigen group, approximately 70% of the whole body's immune cells are accumulated in the gut. The intestinal immune system selectively permits the survival of bacteria that are favorable to the body by way of a complex immune response to the gut microbiota and maintains the diversity of gut microbiota to control exogenous pathogenic bacteria. A reduction in the diversity of the gut microbiota leads to a pro-inflammatory state of the intestinal immune system, which renders a person prone to various diseases [14].

The gut microbiota has several physiological roles, including the promotion of energy production, peristalsis, and digestion–absorption, and contributes to the regulation of metabolism, infection prevention, immunostimulation, and cancer onset [15]. Of these roles, infection prevention and immunostimulation are strongly associated with the mechanism underlying the onset of illness and preterm labor [16]. The infection prevention mechanism involves competition with exogenous pathogenic bacteria for nutrients, inhibition of pathogenic bacterial adhesion to the intestinal epithelium, and inhibition of growth through the production of antibacterial substances and short-chain fatty acids such as acetate and butyric acid [16]. Immunostimulation contributes to increased immunoglobulin A production by the gut microbiota, macrophage activation, and natural immunity activation [16]. Furthermore, the characteristic immune response differs depending on the type of bacteria: intraintestinal segmented bacteria induce T helper 17 cells [17], which exacerbate inflammation, whereas *Clostridium* induces regulatory T cells (Tregs) that alleviate inflammation [15].

Gut microbiota may also cause intrauterine infection, in which ascending and intestinal epithelial hematogenous infection occurs [1]. As mentioned previously, approximately 90% of cases of infection-induced preterm labor are caused by ascending infection and thus abnormal vaginal microbiota is considered to be a major cause of preterm labor. However, metagenomic analysis revealed no difference between the vaginal microbiota during early pregnancy in women who delivered at full-term and that in women who delivered at preterm [17]. In contrast, it has

been reported that changes in gut microbiota are correlated with preterm labor [18], and the relationship between a pro-inflammatory state induced by reduced diversity of the gut microbiota and preterm labor has drawn attention.

14.5 Breakdown of Immunological Tolerance and Preterm Labor

Maintenance of gut microbiota, with the establishment of pregnancy, contributes to peripheral immune tolerance [16]. Immune tolerance includes central tolerance and peripheral tolerance; the former is developed in the thymus and refers to immune tolerance to self-antigens, whereas the latter is developed in peripheral tissues and refers to immune tolerance to non-self antigens. The gut microbiota and fetus are both non-self; thus, their survival necessitates peripheral tolerance. In essence, this involves the inhibition of helper T cells by the proliferation of Tregs [15]. Tregs are immune cells classified into CD4+ and CD25+ T cells, which regulate immune response and express a transcription factor called FoxP3 that is required for their development and function [16]. In the presence of IL-2 and transforming growth factor (TGF)-β, Tregs are induced from immature T cells, and their primary role is the prevention of inflammation by way of regulatory receptors such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death protein 1 (PD-1) and secretion of anti-inflammatory cytokines (IL-10 and IL-4) [15]. Antigen-presenting cells that recognize chorionic villus tissue and members of the gut microbiota (such as *Clostridium* and *Bacteroides*) secrete abundant IL-2 and TGF-β, induce Tregs, and enable the fetus and gut microbiota to escape host immunity [19]. Furthermore, Tregs are induced by acetate and butyric acid produced by the gut microbiota. In pregnant women, Tregs are abundant in the decidua near the villus tissue, i.e., the feto–maternal interface, and they protect the fetus from overactive maternal immunity. Decrease in the number of Tregs leads to the diminution of immune tolerance (Table 14.1), which leads to the activation of various immune cells and an alteration in the intrauterine environment from the anti-inflammatory to the pro-inflammatory state. This consequently activates the labor mechanism, causing uterine contractions and the end of pregnancy [15]. In fact, it has been found that the level of maternal serum IL-10 is decreased in cases of preterm labor [20], and the number of Tregs in the decidua is also reduced [21]. Moreover, the placental capacity to secrete IL-10 during preterm labor is poorer than that during the equivalent period of normal pregnancy [22], which suggests a relationship between preterm labor and reduced immunoregulation.

14.6 Preventing Preterm Labor Using Probiotics

It has been reported that the habitual consumption of probiotics by pregnant women is inversely related to the rate of preterm labor [23]. In a study involving pregnant women who were orally administered a combination of *Lactobacillus, Bifidobacterium,* and *Streptococcus,* it was noted that these women exhibited

elevated levels of IL-4 and IL-10 with low levels of inflammation-inducing chemokines; thus, probiotics amplified the anti-inflammatory state [24]. These results show that probiotics help to inhibit preterm labor, and to date, the administration of probiotics such as *Lactobacillus* has been investigated in several studies. The results have shown an improvement in the incidence of vaginosis; however, preterm labor could not be prevented [4]. Also, the results of a recent meta-analysis did not indicate that probiotics prevents preterm labor [3].

Various probiotics have been evaluated; however, the risk ratios for preterm labor before the 34th week of pregnancy were as follows: 1.03 (95% confidence interval [CI], 0.29–3.64) for *Lactobacillus* (five studies with 1017 subjects), 1.54 (95% CI, 0.27–8.73) for *Bifidobacterium* (three studies with 377 subjects), and 1.60 (95% CI, 0.20–12.69) for *Streptococcus* (two studies with 146 subjects). These ratios are problematic in that the confidence interval was broad and major differences existed among all the studies in the bacteria used, patient background, time when usage began, and usage duration.

In recent retrospective studies involving pregnant women with a history of preterm labor and those at high risk for cervical shortening, the administration of *Clostridium* early on during pregnancy was shown to reduce the incidence of preterm delivery before the 32nd week of pregnancy [25]. *Clostridium* has been found to be a potent inducer of Tregs in the intestinal immune system [26]. It has also been reported that the levels of *Clostridium* and *Bacteroides* and probiotics in the gut microbiota are reduced in pregnant women who experience preterm labor [17], which is very interesting and suggests that gut microbiota plays a role in preventing preterm labor.

14.7 Conclusions

Research regarding the gut microbiota has a short history, and bacteriological examination has shifted to the new field of metagenome analysis, which involves comprehensive and exhaustive examination. Pregnancy and gut microbiota share one physiological characteristic, i.e., their establishment and maintenance depend on peripheral tolerance. We believe that this relationship will be clarified further with advances in testing methods. The effect of probiotics on preterm labor has not yet been fully analyzed, and to clarify the therapeutic effects of probiotics, a randomized controlled trial that takes into account the type of probiotic preparation, starting time, administration duration, and other factors is needed.

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Progesterone

15

Keiya Fujimori, Hyo Kyozuka, and Shun Yasuda

Abstract

Progesterone has been widely used for the prevention of preterm births (PTBs). However, progesterone supplement therapy is considered ineffective for women in preterm labor diagnosed strictly with regular uterine contractions and cervical ripening.

Recent studies have shown that the efficacy of progesterone therapy for preventing PTB may depend on the administration route, type of supplementation, and indication.

First, a detailed medical history should be taken regarding the existence of a prior spontaneous singleton PTB. If a prior singleton PTB is noted, weekly intramuscular (IM) injections of 250 mg of 17-alpha-hydroxyprogesterone caproate (17α-OHPC) from 16 to 20 weeks' gestation until 36 weeks' gestation should be recommended.

Universal screening with transvaginal ultrasonography to detect the cervical length (CL) at 18–24 weeks should be offered to all pregnant women without a prior PTB. If the CL is less than 25 mm, the daily administration of a vaginal progesterone suppository (200 mg) until 36 weeks' gestation should be recommended.

In multifetal pregnancies, the administration of progesterone (either IM or vaginal) does not appear to reduce the incidence of PTB or improve neonatal outcomes. However, in twin pregnancies with a short cervix, vaginal progesterone supplement therapy may be effective in reducing the rate of PTB and improving neonatal outcomes.

According to the Japan health insurance system, 17α-OHPC injections can be used weekly to treat threatened abortion or preterm labor, at a maximum dose of

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125 mg, whereas a natural micronized vaginal progesterone suppository can be used to legally treat infertile patients; however, this treatment is not covered by the health insurance for PTB prevention.

Keywords
Preterm birth · Prevention · Progesterone · 17-alpha-hydroxyprogesterone caproate

15.1 Introduction

Every year, an estimated 15 million babies are born preterm, comprising 11.1% of all live births worldwide and ranging from about 5% in several European countries to 18% in some African countries [1]. Preterm births (PTBs) comprise 5.6% of all births in Japan [2]. The time trends for PTB rates were estimated for 65 countries in the developed nations, Latin America, and the Caribbean regions, with more than 10,000 births in the year 2010 [1]. The mean estimated PTB rate in these countries in 1990 was 7.5% compared to 8.6% in 2010 [1]. Despite many trials regarding tocolytic therapy, antibiotic therapy, and other strategies for prevention, no effective and reproducible method for preventing PTB has been demonstrated [3] and, in most of these countries, including Japan, the PTB rate had been increased in 2010 compared to that in 1990 [1, 2].

However, it is believed that the most effective treatment for PTB is prediction and prevention, depending on its risks. The risk factors for PTB include a history of PTB, short cervical length (CL), multifetal pregnancy, maternal age (<19 and >35 years), infectious diseases, genetic factors, smoking, uterine anomaly, and history of dilatation and curettage or cervical conization [4]. Among these risk factors, a history of PTB and a short CL, usually defined as CL <25 mm on transvaginal ultrasound, are the most important [4].

Progesterone was formerly used as a standard medication for threatened abortion or PTB prevention. Because most obstetricians have been interested in tocolytic agents and infection control for the treatment of preterm labor, progesterone therapy is being decreasingly used for PTB. Since progesterone therapy is cheap and convenient for outpatients, it has been recently reconsidered and reviewed. In 2003, two randomized double-blind placebo-controlled trials demonstrated that progesterone therapy can prevent PTB in women with a history of PTB [5, 6]. Thereafter, many studies and meta-analyses were conducted to reevaluate the efficacy or to add new evidence concerning the prevention of PTB with progesterone therapy. The American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the use of progesterone therapy for PTB prevention in selected pregnant women who have a history of spontaneous PTB, including cases of premature rupture of the membranes, and a short CL identified on transvaginal ultrasound at the mid-trimester [7, 8].

In this chapter, we introduce evidence regarding the use of progesterone supplement therapy for the prevention of PTB, depending on the administration route, type of supplementation, and indication.

15.2 Progesterone Supplementation

Progesterone has been used in two supplementation types, a naturally produced (natural micronized progesterone) or synthetic hormones [17-alpha-hydroxyprogesterone caproate (17α-OHPC)], and via two routes of administration, intramuscularly or vaginally. The supplement, 17α-OHPC, is a synthetic derivative of 17-hydroxyprogesterone. The half-life of 17α-OHPC is 7.8 days [9]; therefore, it is usually administered intramuscularly once a week to maintain serum concentrations. In the Japan health insurance system, 17α-OHPC injections can be used weekly to treat threatened abortion or preterm labor at a maximum dose of 125 mg. Micronized progesterone, a natural progesterone, can be self-administered, as an oral capsule, vaginal gel, or vaginal suppository. When micronized progesterone is administered orally, it is metabolized quickly in the liver and loses its potency. When micronized progesterone is administered vaginally, avoiding metabolism in the liver, it acts on the uterus directly and maintains in a high serum level [9–11].

The mechanism of action of progesterone for PTB prevention is poorly understood. Several investigators have reported the effects of progesterone on PTB, including a decrease in oxytocin receptivity [12–14], anti-inflammatory action [15], and reduced cervical maturation [16]. As there is little evidence regarding the efficacy of progesterone in reducing uterine contractions [17], progesterone supplement therapy is considered ineffective for women in preterm labor diagnosed strictly with regular uterine contractions and cervical ripening.

Concerning maternal and fetal safety, it has not been proven that progesterone causes fetal anomaly. The Food and Drug Administration (FDA) classified natural micronized progesterone medications as category B for pregnancy [18]. The National Institute of Child Health and Human Development (NICHD) study showed there were no significant increases in the rate of miscarriages and stillbirths in the progesterone group compared with the placebo group [5]. An observational follow-up study also reported no significant difference in long-term infant outcomes between progesterone and placebo groups [19, 20]. Moreover, in 2011, FDA approved 17α-OHPC for the reduction of PTB in women with a history of PTB [21].

15.3 Screening Algorithm for Predictive Risk Factors (Fig. 15.1)

The risk factors for PTB include a history of spontaneous PTB, short CL, multifetal pregnancy, maternal age, infectious diseases, genetic factors, smoking, uterine anomaly, and a history of dilatation and curettage or cervical conization [4]. Among the risk factors, a history of spontaneous PTB and a short CL are the most important.

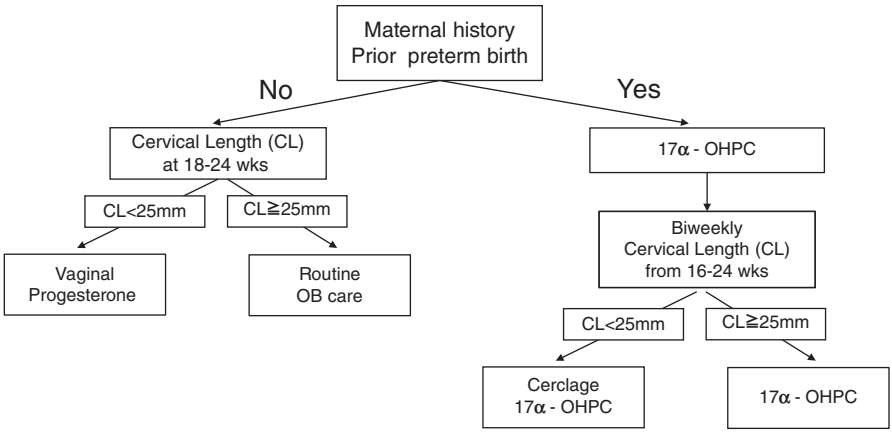

Fig. 15.1 Algorithm for progesterone use in singletons to prevent preterm birth

An accurate history should be taken regarding the risk factors for PTB. A detailed maternal history includes whether the prior PTB was spontaneous or indicated. Spontaneous PTB is defined as PTB prior to 37 weeks caused by preterm labor, premature rupture of the membrane, or cervical insufficiency. The evaluation of women with a prior spontaneous PTB or mid-trimester abortion should include a detailed medical history, comprehensively reviewing all previous pregnancies and the risk factors, and determining their candidacy for prophylactic interventions such as progesterone supplementation, cervical cerclage, or both. A previous spontaneous PTB is commonly reported to confer a 1.5–2-fold increased risk of PTB in subsequent pregnancies [7]. The recurrence rate significantly increases with a shorter gestational age in the previous PTB and an increase in the number of previous PTBs. A previous term delivery confers a lower risk than the aforementioned situations [22, 23].

Another important method for predicting the risk for PTB is the measurement of CL by vaginal ultrasound during the mid-trimester [4, 7, 24, 25]. Transvaginal ultrasonography has been shown to be a reliable and highly reproducible method for assessing the length of the cervix. Screening with transvaginal ultrasound CL at around 18–24 weeks should be offered for all asymptomatic singleton pregnancies. The risk of PTB is substantially high when CL is <25 mm, and the risk increases as CL decreases. Therefore, in randomized trials studying the efficacy of progesterone supplement therapy for preventing PTB, a short CL was another major indication for therapy.

Progesterone supplement therapy is one of the few proven methods that are effective for preventing PTB in women with a history of spontaneous PTB and in women with a short CL.

15.3.1 17α-OHPC for a History of PTB

In a 2003 NICHD report, Meis et al. conducted a randomized double-blind multicenter trial to evaluate the effectiveness of 17α-OHPC in women with a PTB history for the prevention of PTB in subsequent pregnancies [5]. Women who were enrolled at 16–20 weeks of gestation received either weekly intramuscular injections of 250 mg of 17α-OHPC or weekly injections of a placebo; the injections were continued until delivery or 36 weeks of gestation. Treatment with 17α-OHPC significantly reduced the risk of delivery at <37 weeks [relative risk (RR) 0.66, 95% confidence interval (CI) 0.54–0.81], <35 weeks (RR 0.67, 95% CI 0.48–0.93), and <32 weeks (RR 0.58, 95% CI 0.37–0.91) of gestation. Infants of women treated with progesterone had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. They concluded that weekly injections of progesterone resulted in a substantial reduction in the rate of recurrent PTB among women who had a particularly high risk for PTB and reduced the incidence of several complications in their infants. After this study, another randomized trial, reported by Saghafi et al., also showed that 17α-OHPC treatment was associated with a significantly lower rate of PTB at less than 37 weeks of gestation [26].

As shown in Table 15.1, a meta-analysis of four randomized controlled trials (RCTs) also showed the benefit of weekly intramuscular 17α-OHPC in terms of the reduction of PTB at <37 weeks' gestation (RR 0.62, 95% CI 0.52–0.75) and the reduction of perinatal mortality (RR 0.41, 95% CI 0.23–0.73) in women with a previous PTB [27].

Table 15.1 Meta-analysis of progesterone versus placebo/no treatment in singletons with a previous history of spontaneous preterm birth

Outcome	No. of studies	No. of participants	Risk ratio (M-H, fixed, 95% CI)
Preterm birth <37 weeks	10	1750	0.55 [0.42, 0.74]
Intramuscular	4	652	0.62 [0.52, 0.75]
Vaginal	5	1065	0.52 [0.29, 0.92]
Oral	1	33	0.46 [0.19, 1.11]
Preterm birth <34 weeks	5	602	0.31 [0.14, 0.69]
Intramuscular	0	0	0.0 [0.0, 0.0]
Vaginal	4	454	0.21 [0.10, 0.44]
Oral	1	148	0.59 [0.39, 0.90]
Perinatal mortality	6	1453	0.50 [0.33, 0.75]
Intramuscular	3	553	0.41 [0.23, 0.73]
Vaginal	2	752	0.67 [0.34, 1.29]
Oral	1	148	0.43 [0.12, 1.59]

CI confidence interval

In summary, for singleton pregnancies with more than one previous spontaneous PTB, weekly intramuscular injections of 17α-OHPC 250 mg from 16 to 20 weeks' gestation until 36 weeks' gestation should be recommended.

15.3.2 Vaginal Progesterone for a History of PTB

In 2003, at the same time as the Meis et al. report, da Fonseca et al. reported the result of a randomized double-blind trial on vaginal natural micronized progesterone suppository therapy in singleton pregnancies, a majority of whom (>90%) had a previous PTB [6]. Nightly administration of vaginal progesterone (100 mg) from 24 to 34 weeks was associated with a significant reduction in the incidence of PTB (<37 weeks) (RR 0.48, 95% CI 0.25–0.96) [6]. In another randomized study reported by O'Brien et al. in 2007, 659 women with singleton pregnancies who had a previous PTB (20–35 weeks) were administered 90 mg of vaginal natural micronized progesterone gel daily starting at 18–23 weeks' gestation [28]. The vaginal progesterone gel did not reduce the incidence of PTB at <37, <36, <33, and <29 weeks or improve neonatal outcomes. However, in a secondary analysis of women with CL <28 mm, the progesterone gel treatment was associated with a significantly lower rate of PTB at <32 weeks of gestation. Several women screened for this trial were excluded because of a short CL; therefore, there is, at present, stronger evidence of the effectiveness of 17α-OHPC compared to vaginal progesterone.

As shown in Table 15.1, a meta-analysis of five RCTs also showed the benefit of vaginal progesterone in women with a previous PTB for the reduction of PTB<37 weeks (RR 0.52, 95% CI 0.29–0.92) and <34 weeks (RR 0.21, 95% CI 0.10–0.44) and with no reduction of perinatal mortality (RR 0.67 95% CI 0.34–1.29) [27]. Vaginal progesterone, thus, seems to have an equivalent, if not greater, effectiveness as 17α-OHPC.

15.3.3 17α-OHPC for a Short CL

Regarding 17α-OHPC, a multicenter RCT evaluating the effect of 17α-OHPC compared with placebo in women with singleton gestations, no prior PTB, and short CL <30 mm showed no difference in the rate of PTB at <37 weeks (RR 1.03, 95% CI 0.79–1.35) [29].

In another later study, pregnant women at high risk for PTB (prior PTB, cervical surgery, uterine malformation, or prenatal diethylstilbestrol exposure) and CL <25 mm were randomized to weekly intramuscular injections of 500 mg of 17α-OHPC or no treatment. There were no significant differences between the groups [30].

In summary, 17α-OHPC cannot be recommended for the prevention of PTB in singleton pregnancies with a short CL and without prior PTB.

15.3.4 Vaginal Progesterone for a Short CL

Several RCTs have been conducted to evaluate the efficacy of vaginal progesterone on asymptomatic cervical shortening cases. In 2007, the Fetal Medicine Foundation in the UK showed the effects of vaginal progesterone on women with a short cervix [31]. This trial enrolled 250 women mostly (90%) with singleton pregnancies and a very short CL (<15 mm at 20–24 weeks) and demonstrated a lower risk for PTB in those treated with vaginal progesterone suppository, 200 mg nightly, started at 24–34 weeks, compared with those treated with a placebo. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (RR 0.56, 95% CI 0.36–0.86). However, there were no significant effects on composite neonatal adverse outcomes (RR 0.57, 95% CI 0.23–1.31) [31]. In a subsequent randomized trial, the use of vaginal progesterone gel, 90 mg daily, was associated with a decrease in spontaneous PTB at <33 weeks of gestation (RR 0.55, 95% CI 0.33–0.92) and a decrease in neonatal morbidity and mortality (RR 0.57, 95% CI 0.33–0.99) among asymptomatic singleton-pregnant women with a CL of 10–20 mm at 19–24 weeks of gestation [32]. In this study, an analysis of only women without prior PTB confirmed a significant benefit of progesterone in preventing PTB before 33 weeks of gestation. However, a very recent multicenter randomized double-blind trial of vaginal progesterone therapy (OPPTIMUM study) showed contradictory results [33]. In this trial, 1228 high-risk women (history of PTB <34 weeks, CL ≤25 mm, or positive fetal fibronectin test with other risk factors for PTB) received 200 mg of vaginal natural micronized progesterone suppository or placebo daily, from 22–24 weeks to 34 weeks of gestation. To date, this study is the largest trial of vaginal progesterone treatment for the prevention of PTB in women at risk; however, it did not show any effects of progesterone treatment on the rates of either PTB or neonatal and infant outcome in the entire study group and all subgroup analyses. These results are conflicting regarding the clinical efficacy of vaginal progesterone for preventing PTB and concerning adverse perinatal outcomes in singleton pregnancies with a short cervix. Therefore, Romero et al. conducted a meta-analysis of five high-quality RCTs, including the OPPTIMUM study, to clarify whether vaginal progesterone prevents PTB and improves perinatal outcomes in asymptomatic women with a singleton gestation and a mid-trimester sonographic short cervix [20]. This meta-analysis showed the benefit of vaginal progesterone in asymptomatic women with a short cervix detected by vaginal ultrasound (<25 mm) for the reduction of PTB at <33 weeks' gestation (RR 0.62, 95% CI 0.47–0.81) (Fig. 15.2) and for improving neonatal outcomes (RRs from 0.47 to 0.82). Moreover, vaginal progesterone significantly decreased the risk of PTB at <36, <35, <34, <32, <30, and <28 weeks of gestation [20].

In summary, in women with singleton gestations, no prior PTB, and short CL, vaginal progesterone is associated with a reduction in PTB and improved neonatal outcomes. If CL <25 mm is identified at <24 weeks, vaginal progesterone should be offered for PTB prevention. There is insufficient evidence indicating that any type of vaginal progesterone or doses is superior.

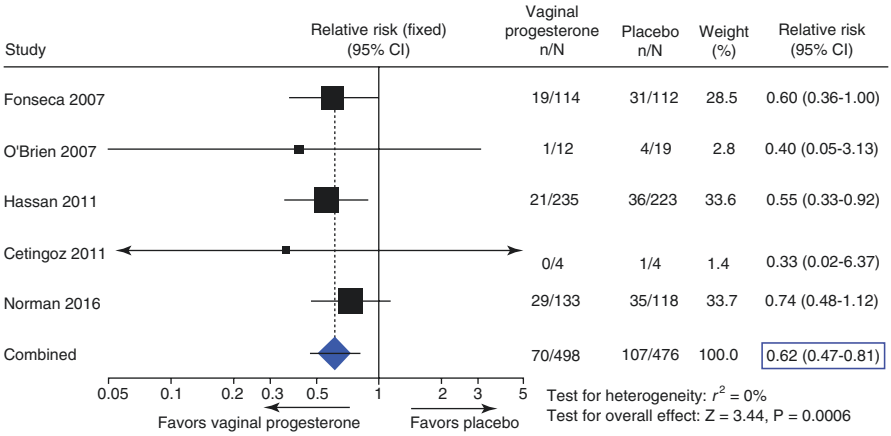

Fig. 15.2 Meta-analysis of the effect of vaginal progesterone on preterm birth at <33 weeks of gestation in singleton pregnancies with a short cervix. *CI* confidence interval

Table 15.2 Meta-analysis of prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy

Outcome	No. of studies	No. of participants	Risk ratio (M-H, fixed, 95% CI)
Intramuscular (IM) progesterone versus no treatment or placebo			
Preterm birth <37 weeks	5	2010	1.05 [0.98, 1.13]
Preterm birth <34 weeks	2	399	1.54 [1.06, 2.26]
Preterm birth <28 weeks	5	1920	1.08 [0.75, 1.55]
Perinatal death	6	3089	1.45 [0.60, 3.51]
Vaginal progesterone versus no treatment or placebo			
Preterm birth <37 weeks	6	1597	0.97 [0.89, 1.06]
Preterm birth <34 weeks	6	1727	0.83 [0.63, 1.09]
Preterm birth <28 weeks	4	1569	1.22 [0.68, 2.21]
Perinatal death	3	2287	1.23 [0.74, 2.06]
Intramuscular (IM) progesterone versus no treatment: multiple (twin) pregnancy with a short cervix			
Preterm birth <37 weeks	1	161	1.06 [0.90, 1.25]
Preterm birth <34 weeks	1	161	1.67 [1.04, 2.68]
Perinatal death	1	330	9.11 [1.17, 71.10]
Vaginal progesterone versus no treatment: Multiple (twin) pregnancy with a short cervix			
Preterm birth <34 weeks	1	224	0.67 [0.49, 0.91]
Preterm birth <28 weeks	1	224	0.37 [0.07, 1.88]
Respiratory distress syndrome	1	439	0.68 [0.55, 0.84]

15.4 Progesterone for Multiple Pregnancy

Multiple pregnancy is a strong risk factor for PTB, and more than 50% of women with a twin pregnancy will give birth prior to 37 weeks' gestation.

As shown in Table 15.2, a recent meta-analysis also showed that both intramuscular 17α-OHPC and vaginal progesterone supplement therapy were ineffective for

the reduction of PTB and for improving perinatal outcomes in unselected women with uncomplicated multiple pregnancies [34]. However, natural micronized vaginal progesterone suppository, but not intramuscular 17α-OHPC [35], may be effective for the reduction of PTB at <34 weeks' gestation and adverse perinatal outcomes in twin-pregnant women with a CL ≤25 mm [36]; nevertheless, there is insufficient evidence to recommend this study. Further studies are needed to evaluate the efficacy of vaginal progesterone in multiple pregnancies with short CL.

In unselected women with multiple pregnancies, the administration of progesterone (either intramuscular or vaginal) does not appear to reduce the incidence of PTB or to improve neonatal outcomes. However, in a case of twin pregnancies and a short cervix, vaginal progesterone supplement therapy may be effective for reducing the rate of PTB and for improving neonatal outcomes.

15.5 Japan Prospective Study (TROPICAL STUDY: Trial of Progesterone Vaginal Tab in the Prevention of Preterm Delivery Evaluated by Cervical Length)

In Japan, 17α-OHPC injections administered weekly at a maximum dose of 125 mg are covered under health insurance. However, a natural micronized vaginal progesterone suppository for infertile patients can legally be used, but is not underwritten by health insurance for PTB prevention and medication for preterm labor.

Currently, in Japan, a multicenter collaborative, double-blind, placebo-controlled, randomized parallel-group comparison trial has been conducted for 3 years since 2014. This RCT aims to evaluate the effect of daily natural micronized progesterone suppository therapy (Cyclogest 200 mg) in women with a short CL in reducing PTB. Women with singleton pregnancies and CL < 30 mm at 16–24 weeks' gestation were enrolled and serial measurements of CL were carried out biweekly. This trial should provide new evidence from Japan regarding the prevention of PTB.

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Cerclage 1: General

16

Kaori Michikata and Hiroshi Sameshima

Abstract

Cervical cerclage is a procedure that has been used to prevent preterm birth. The efficacy and safety of this procedure remain controversial. Some reviews recommend cerclage for women with singleton pregnancy, history of prior spontaneous preterm delivery, and short cervix.

Keywords

Cervical cerclage · Prior preterm birth · Cervical length · Vaginal ultrasonography · Perinatal outcome

16.1 Introduction

Cervical cerclage is a procedure that has been used to prevent preterm birth. Controversy regarding the indications, efficacy, and safety of cerclage exists in the medical literature. In a systematic review of cervical cerclage in singleton pregnancies in 2017 [1], the risk of preterm births was reduced, but serious neonatal morbidity and intact neonatal survival were similar, with and without cerclage. Although the number of trials based on clinical indication has been too limited to make meaningful conclusions, some studies noted the effects of cerclage in particular circumstances.

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16.2 Indication

There are three circumstances where cerclage may be used to prevent preterm birth. First, history-indicated cerclage (known as prophylactic cerclage) is performed in women who have a history suggestive of cervical insufficiency, such as one or more second-trimester pregnancy losses related to painless cervical dilatation in the absence of labor or abruptio placentae. Second, ultrasound-indicated cerclage, which is performed in women identified to have a short cervix on transvaginal ultrasonography. Third, physical examination-indicated cerclage (known as emergency or rescue cerclage), which is performed in women found to have a significantly short or dilated cervix on vaginal examination.

16.2.1 History-Indicated Cerclage

Cervical insufficiency is the term used to describe cervical dilatation without the signs and symptoms of clinical contractions or labor in the second trimester. There are no clear criteria for this diagnosis. Patient selection is based on a history of painless cervical dilatation in the second trimester. Three randomized controlled trials have reported on the efficacy of history-indicated cerclage. Two of these trials that compared cerclage with no cerclage for 194 and 506 women, respectively, who had a history of a late abortion or a preterm delivery found no improvement in perinatal outcome in the cerclage groups [2, 3]. The third trial was an intent-to-treat study of 1292 women at risk of preterm delivery, most of whom had a history of early delivery or cervical surgery [4]. They found that there were fewer deliveries before 33 weeks (83 [13%] compared with 110 [17%], $P = 0.03$), increased medical intervention, and a doubling of the risk of puerperal pyrexia in the cerclage group.

16.2.2 Ultrasound-Indicated Cerclage

Transvaginal ultrasound examination is used for women with risk factors for preterm delivery. Recent summaries of multiple studies, which are limited to singleton pregnancies, showed that ultrasound-indicated cerclage for women with prior spontaneous preterm birth improved maternal and perinatal morbidity. A randomized trial in women with prior spontaneous preterm birth before 34 weeks and cervical length <25 mm detected before 23 weeks showed that cerclage reduced birth before 35 weeks in the women with cervical length <15 mm, previable birth (before 24 weeks), and perinatal mortality [5].

A meta-analysis showed that in women with previous spontaneous preterm birth and cervical length <25 mm before 24 weeks, cerclage reduced preterm birth before 35 weeks and composite perinatal mortality and morbidity [6].

On the other hand, cerclage in women without a history of prior spontaneous preterm birth and with cervical length <25 mm detected between 16 and 24 weeks did not reduce the preterm birth significantly [7].

16.2.3 Physical Examination-Indicated Cerclage

A meta-analysis of ten studies (one randomized control study, two prospective cohort studies, and seven retrospective cohort studies) comparing cerclage placement with expectant management of women with cervical dilatation of 0.5 cm or greater between 14 and 27 weeks of gestation reported that cerclage was associated with increased neonatal survival and prolongation of pregnancy [8]. Majority of patients in this study were from nonrandomized trials and the potential for bias is strong because clinicians may have opted for expectant management in patients they deemed to be at higher risk for short-term delivery. A study of 116 women who underwent emergency cerclage between 16 and 24 weeks showed that nulliparity, the presence of membrane prolapse beyond the external cervical os, and cerclage placement before 22 weeks are associated with a significantly decreased chance of pregnancy continuation to 28 weeks or beyond [9].

16.2.4 Other Indications

In a systematic review of five randomized controlled trials of cervical cerclage in multiple pregnancies, there is no evidence for the effectiveness of cerclage in preventing preterm births and reducing perinatal death or neonatal morbidity [10].

There is no evidence for the benefit of cerclage in patients with prior cone biopsy, loop electrosurgical excision procedure, or Müllerian anomaly [11].

16.3 Procedures

There are two commonly performed cerclage procedures. The simpler procedure was developed by McDonald [12]. The operation described by Shirodkar is more complicated [13]. A study comparing the efficacy of the two procedures in women with sonographically detected short cervix found no significant difference in the prevention of preterm birth before 33 weeks [14]. Some practitioners place an additional stitch at the time of the initial cerclage procedure. A retrospective cohort study of women who underwent history- or ultrasound-indicated cerclage found that two stitches did not improve pregnancy outcome compared with one stitch [15].

Prophylactic cerclage is typically placed between 12 and 14 weeks. Ultrasound-indicated cerclage in high-risk women is placed at the time of detection of cervical shortening, usually before 24 weeks. When the cervical shortening or dilatation is detected after 23 weeks, there is debate as to whether emergency cerclage should be performed. Although emergency cerclage is not recommended at gestational ages when intact neonatal survival is expected, the decision depends on each institution.

Perioperative antibiotics and prophylactic tocolysis do not improve the efficacy of cerclage [11]. When gonorrhea, chlamydia, and other obvious cervical infections are detected on preoperative screening, these are treated with adequate antibiotics [16].

Cerclage removal is recommended at 36–37 weeks in patients with no complications.

16.4 Complications

Complications of cerclage are rupture of membranes, preterm labor, hemorrhage, infection, and cervical laceration. These are all uncommon with history- or ultrasound-indicated cerclage. In the multicenter study comparing an ultrasound-indicated cerclage group with an expectant management group, of the 153 patients who underwent cerclage, two complications were noted: one patient had membrane rupture during the procedure and the other had postoperative hemorrhage [5].

In a meta-analysis of physical examination-indicated cerclage, the incidence of intraoperative membrane rupture was 4.1% and cervical laceration was 7.9% in women who underwent cerclage with cervical dilatation, but these data were not reported for the expectant management group [8].

The decision to remove or retain a cerclage in patients with subsequent preterm premature rupture of membranes (PROM) is controversial. In some retrospective studies, cerclage retention with preterm PROM was associated with increased risk of neonatal sepsis, respiratory distress syndrome, neonatal mortality from sepsis, and maternal chorioamnionitis [17]. A prospective randomized multicenter trial showed that statistically significant differences were not seen in prolongation of latency, infection, or composite neonatal outcomes between removal and retention of cerclage. However, they concluded that the data might suggest no advantage to retaining cerclage after preterm PROM and a possibility of increased infection with cerclage retention [18].

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Cerclage 2: Abdominal vs Vaginal

17

Keiko Akeno

Abstract

Cervical cerclage to prevent preterm labor in cervical incompetence is performed transvaginally or transabdominally, with the transvaginal method generally used. Transabdominal cerclage is a more invasive procedure than transvaginal cerclage and is performed in patients for whom transvaginal cerclage is difficult. It is recommended that the transvaginal procedure be performed at 12–14 weeks of pregnancy and that transabdominal cerclage be performed up to week 12. Although both procedures carry a risk of hemorrhage and premature rupture of the membranes, with transabdominal cerclage in particular there is a risk of problems such as adhesion formation resulting from repeated laparotomy. In managing postoperative care after both procedures, caution is exercised with respect to symptoms of threatened miscarriage or preterm labor. Although the suture is removed at 36–37 weeks of pregnancy with transvaginal cerclage, transabdominal cerclage requires laparotomy to remove the suture, and delivery is therefore performed by Cesarean section. It has been noted that, in patients with a disturbance of the vaginal flora, transvaginal cerclage may worsen local infection and increase the rate of preterm labor. Because transabdominal cerclage can be performed under sterile conditions, it may be useful in patients with local infection.

Keywords

Cervical cerclage · Transvaginal cerclage · Transabdominal cerclage

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17.1 Introduction

Cervical cerclage is a surgical therapy performed to prevent preterm labor in patients with cervical incompetence. Among the cervical cerclage procedures, transvaginal cerclage is the one typically performed, but cervical cerclage is also performed under laparotomy. The types of transvaginal cerclage are the Shirodkar and McDonald procedures, both developed in the 1950s [1, 2]. Transabdominal cerclage is a surgical therapy for intractable cervical incompetence that was initially developed in 1965 [3]. This section describes and compares the transvaginal and transabdominal methods.

17.2 Indications and Contraindications

Indications for transvaginal cerclage are a history of miscarriage or preterm labor (history-indicated) of unknown etiology during the second trimester of pregnancy [4], a history of preterm labor and cervical shortening (<25 mm) seen on transvaginal ultrasonography at 16–23 weeks of pregnancy (ultrasound-indicated) [5], and cervical dilation seen on visual inspection or pelvic examination at 16–23 weeks of pregnancy (physical exam-indicated) [6]. Although there have been several reports indicating that either the Shirodkar method or the McDonald method is more effective, there is not strong evidence in favor of either method [7, 8]. Currently, neither procedure is considered superior to the other.

In the case of transabdominal cerclage, laparotomy is required for suture removal, and delivery is therefore performed by Cesarean section. In other words, two laparotomies are required, one for cervical cerclage and one for Cesarean section, which makes this a more invasive procedure than transvaginal cerclage. Indications for transabdominal cerclage are previous miscarriage or preterm labor that occurred despite transvaginal cerclage and difficulty in performing transvaginal cerclage due to cervical shortening, scarring, or laceration [3, 9]. In patients who have undergone extensive cervical resection as a result of conization or abdominal trachelectomy, there is no location to place the cerclage suture, which makes the transvaginal method very difficult. At University of Miyazaki Hospital, transabdominal cerclage is considered indicated if almost no cervical length is present or laceration or other marked deformation of the cervix has occurred, making transvaginal cerclage difficult [10].

The procedure of the transabdominal cerclage is as follows: With the patient supine, laparotomy is performed with a vertical midline incision or Pfannenstiel incision in the lower abdomen. The peritoneal reflection of the vesicouterine pouch is then incised, the urinary bladder detached, and the lower part of the uterus exposed. The uterine artery pulse is palpated, and the uterine artery and vascular plexus are gently moved laterally to obtain an avascular field. A Shirodkar suture with a needle at each end is used to place a suture in the cervical stroma from anterior to posterior at the level of the internal orifice of the uterus. This operation is performed on both the left and right sides. The Shirodkar suture is tied posterior to

the uterus, the peritoneal incision is closed by suturing, and the abdomen is closed. Cervical cerclage is also performed laparoscopically, and the outcomes are comparable to those obtained by laparotomy [11].

Similar contraindications apply to both transvaginal and transabdominal cerclage. The contraindications are as follows: active genital bleeding, intrauterine infection, amniorrhexis (amniotic fluid leakage), fetal death in utero, or a lethal fetal anomaly, because cervical cerclage does not reduce the risk of preterm labor or improve the fetal outcome.

17.3 Timing

Of the different types of transvaginal cerclage, it is recommended that history-indicated prophylactic cervical cerclage be performed at 12–14 weeks of pregnancy [4]. The frequency of complications increases as the number of gestational weeks increases and cervical dilation is seen. Before cerclage is performed, ultrasonography is performed to determine whether the size of the fetus corresponds to the weeks of gestation and whether a fetal malformation is present.

It is recommended that transabdominal cerclage be performed before pregnancy or in the first trimester, especially up to the 12th week of pregnancy [12, 13]. Because the uterus increases in size as the number of gestational weeks increases, the transabdominal cerclage procedure becomes difficult after the first trimester, and complications such as hemorrhage increase. Although there have been no randomized studies comparing groups in which transabdominal cerclage was performed before or during pregnancy, a review of 14 studies (678 patients) of transabdominal cerclage published between 1990 and 2013 found the proportion of live births obtained to be comparable [11].

17.4 Complications

Complications rarely occur in patients who undergo history-indicated transvaginal cerclage, having been reported in less than 6% of such patients [4]. Complications that occur are premature rupture of the membranes, intrauterine infection, and suture migration. Premature rupture of the membranes has been reported in approximately 2% of patients who underwent history-indicated transvaginal cerclage [14]. Among patients who undergo physical exam-indicated cerclage, 65% of those with marked cervical dilation or prolapsed fetal membranes have peri- or postoperative premature rupture of the membranes [14]. The proportion with intrauterine infection is between 2% and 25% [14], and serious septicemia has been reported in mothers [15]. Suture migration occurs in 3–13% [16]. In addition, transvaginal cerclage may cause cervical laceration or hemorrhage. The frequency of the above complications increases with the number of gestational weeks and the degree of cervical dilation.

Transabdominal cerclage is a more invasive procedure than transvaginal cerclage and requires particular caution with respect to hemorrhage resulting from vascular injury. Massive hemorrhage that threatens the life of the mother may also occur. The risk of hemorrhage can be minimized by performing the procedure before pregnancy, when the pelvic blood vessels are thin [17]. In addition, inadvertent ligation of the uterine artery may result in fetal death in utero, intrauterine growth restriction, infection, premature rupture of the membranes, or uterine rupture [18, 19]. As was mentioned above, transabdominal cerclage requires two laparotomies, one for cervical cerclage and one for Cesarean section. Consequently, there is also a risk of complications such as adhesions with repeated laparotomy.

17.5 Postoperative Care and Follow-Up

Postoperative management is similar with both the transvaginal and transabdominal cerclage procedures. Postoperatively, after the patient has recovered from anesthesia, activities of daily living (ADL) are gradually expanded, and the patient is discharged after confirming that there are no symptoms of infection or genital hemorrhage and no abnormalities of the fetal heart rate or amniotic fluid volume. However, patients who undergo a physical exam-indicated procedure are at an increased risk of complications such as premature rupture of the membranes and may require long-term hospitalization, depending on the case.

Acetaminophen is prescribed for cervicovaginal pain in the case of transvaginal cerclage and for surgical wound pain in the case of transabdominal cerclage.

After the patient is discharged, particular attention is paid during follow-up to symptoms of threatened miscarriage or preterm labor, such as abdominal pain and genital hemorrhage. If they experience a sensation suggestive of amniorrhexis, the patient is instructed to undergo examination because amniorrhexis should be differentiated. Cervical length is measured by transvaginal ultrasonography on an outpatient basis to determine whether shortening has occurred, and the presence of genital hemorrhage and uterine contractions is assessed. Although the frequency of uterine contractions is increased in patients who have undergone cervical cerclage [4], this may not be associated with an increased risk of preterm labor. As mentioned previously, a complication of transabdominal cerclage is intrauterine growth restriction. Consequently, attention is paid to the growth status of the fetus during patient follow-up.

17.6 Cerclage Removal and Delivery

With transvaginal cerclage, suture removal is performed at 36–37 weeks of pregnancy. If labor pain begins before that time and preterm labor is imminent, suture removal must then be performed to prevent cervical laceration and uterine rupture. Although suture removal can be performed on an outpatient basis without anesthesia, in the case of the Shirodkar method, it occasionally must be performed in an

operating room under anesthesia. After suture removal, the patient is allowed to go home and wait until the onset of labor pain. Only approximately 10% of patients have been reported to give birth by natural delivery within 48 h after suture removal [20]. If it is decided that delivery will be performed by Cesarean section for a reason such as the patient's having a previous history of Cesarean section, suture removal is not performed at 36–37 weeks of pregnancy but rather after the Cesarean section while the patient is anesthetized.

There are pros and cons regarding suture removal if preterm premature rupture of the membranes (PPROM) occurs [21–25]. While there is the view that suture removal results in premature delivery, there is also the view that the risk of infection is increased by leaving the cerclage suture in place. In a randomized study examining whether the cerclage suture should be removed or left in place in the case of PPROM, no difference in pregnancy outcomes was seen between the groups, although the study was small (prolongation of pregnancy by 1 week or longer: 56.3% in the suture removal group vs. 45.8% in the group with suture left in place, $p = 0.59$; chorioamnionitis: 25.0% in the suture removal group vs. 41.7% in the group with suture left in place, $p = 0.25$) [26].

In the case of transabdominal cerclage, as mentioned above, laparotomy is required for suture removal, and delivery is therefore performed by Cesarean section. Suture removal is performed after the fetus is delivered by Cesarean section. Although subsequent pregnancies are sometimes planned with the cerclage suture left in place, there are no data on the frequency and outcomes of such pregnancies. Moreover, leaving the suture in place may result in infection or vaginal erosion [27]. In patients who wish to have children again and for whom the risk associated with repeated laparotomy is high and in patients for whom suture removal is difficult, the cerclage suture is left in place and complications such as infection are thoroughly explained.

17.7 Transvaginal vs. Transabdominal

Studies comparing outcomes with transvaginal and transabdominal cerclage are still lacking. At University of Miyazaki Hospital and its affiliated institutions, between January 2004 and February 2015, 170 patients underwent cervical cerclage (Shirodkar procedure, 162 patients; transabdominal cerclage, 8 patients) and had a single pregnancy that resulted in delivery. Examination of the gestational age at delivery in the Shirodkar and transabdominal groups showed that miscarriage or preterm labor occurred in 10 of the 162 patients (6.2%) in the Shirodkar group at 24 gestational weeks or earlier, while 1 of the 8 patients (12.5%) in the transabdominal group had a miscarriage at 22 weeks or earlier. A chi-squared test showed no significant difference between the groups in the rate of miscarriage or preterm labor at 24 weeks or earlier. Closer examination of the 10 patients who underwent the Shirodkar procedure and had a miscarriage or preterm labor at 24 gestational weeks or earlier showed that a disturbance of the vaginal flora had occurred in 7 of these patients. Specifically, there was a decrease in Lactobacillus, part of the normal

Table 17.1 Comparison between abdominal cerclage and vaginal cerclage

	Transvaginal procedure	Transabdominal procedure
Indications	– History of miscarriage or preterm labor (history-indicated) of unknown etiology during second trimester of pregnancy – History of preterm labor and cervical shortening (<25 mm) on transvaginal ultrasonography at 16–23 weeks of pregnancy (ultrasound-indicated) – Cervical dilation on visual inspection or pelvic examination at 16–23 weeks of pregnancy (physical exam-indicated)	– Previous miscarriage or preterm labor that occurred despite transvaginal cerclage – Difficulty performing transvaginal cerclage due to cervical shortening, scarring, or laceration
Contraindications	Active genital bleeding, intrauterine infection, amniorrhexis, fetal death in utero, lethal fetal anomaly	
Timing of procedure	12–14 weeks of pregnancy (history-indicated)	Before pregnancy or during first trimester (up to week 12)
Complications	Premature rupture of the membranes, intrauterine infection, suture migration, hemorrhage, cervical laceration	Hemorrhage (massive), fetal death in utero, intrauterine growth restriction, infection, premature rupture of the membranes, uterine rupture, adhesion
Postoperative management	Can be discharged if symptoms of infection, genital hemorrhage, abnormalities of fetal heart rate, and amniotic fluid volume are absent Pain control Attention paid to symptoms of threatened miscarriage or preterm labor such as abdominal pain, genital hemorrhage during follow-up	
Suture removal, delivery method	Transvaginal delivery: 36–37 weeks of pregnancy Cesarean section: After completion of Cesarean section	After completion of Cesarean section

bacterial flora of the vagina, resulting in the predominance of other bacteria. In addition, 2 of the 10 patients had an old cervical laceration, which made the Shirodkar procedure difficult. According to Sakai et al., if local infection or inflammation is present in the vagina or cervix, cervical cerclage may worsen these conditions and increase the rate of preterm labor [28]. Because transabdominal cerclage can be performed under sterile conditions, it may be useful in patients with local infection of the vagina or cervix.

A summary comparison of the transvaginal and transabdominal methods is shown in Table 17.1.

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Bacterial Vaginosis

18

Midori Fujisaki

Abstract

Bacterial vaginosis (BV) is a risk factor for spontaneous preterm labor and delivery. About 90% of spontaneous preterm births are considered to be ascending infections from the vagina and the remaining 10% are considered to be hematogenous infections. Although considered the best way to reduce spontaneous preterm birth, normalizing the bacterial flora in the vagina has not been proven to prevent spontaneous preterm birth. Based on recent reports, we discuss preterm birth prevention and BV.

Keywords

Bacterial vaginosis · Preterm labor · Vaginal bacterial flora

18.1 Pathogenesis of BV

The vaginal microbiota of normal healthy women is mainly composed of Lactobacillus spp. Lactobacillus decomposes the glycogen contained in vaginal epithelium, produces lactic acid, and keeps the vaginal pH low (<4.5). It prevents the abnormal growth of other organisms including anaerobic bacteria. Imbalances in this microbiota can lead to bacterial vaginosis (BV), one of the most common causes of abnormal vaginal discharge in reproductive age women. With BV, numbers of Lactobacillus spp. are decreased, and anaerobic bacteria increased, including species such as Gardnerella vaginalis, Prevotella spp., Bacteroides spp., Mobiluncus spp., Mycoplasma hominis, and BV-associated bacteria, namely BVAB1, BVAB2,

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and BVAB3. The last three bacteria are newly recognized species [1]. G. vaginalis is the key bacterium in the pathogenesis of BV [2]; it forms a biofilm on the vaginal epithelial cells, and various bacteria such as anaerobes attach to this and grow abnormally. G. vaginalis is also frequently detected in women with normal vaginal flora, so the onset of mechanism is unknown.

18.2 Diagnosis

Culture-based analyses have been used for decades and, in general microbiology, have provided critical knowledge concerning microbes and the understanding of infectious diseases. However, many microbes cannot be cultured because the essential requirements for growth are not known. In recent years, the development of 16s rRNA gene sequences has made it possible to identify the complexity of the microbial ecosystem of various body sites, including the human vagina [3]. The vaginal bacterial flora are classified into five types, referred to as community state types (CSTs), based on differences in species composition. Four of these CSTs (CSTs I, II, III, and V) are most often dominated by one of the four Lactobacillus spp. commonly found in the vagina (L. crispatus, L. iners, L. jensenii, and L. gasseri). In contrast, CST IV is dominated by Prevotella, Sneathia, Megasphaera, Atopobium, or Streptococcus, which are often associated with BV [3–5].

BV commonly occurs in women of reproductive age, and the incidence of BV varies markedly among racial and ethnic groups. In the USA, almost one-third of women (29%) are positive for BV. The prevalence of BV is 50% in African American women, 32% in Mexican American women, and 23% in those of European ancestry [6]. Takahashi et al. retrospectively examined 2158 low-risk Japanese pregnancies before 20 weeks of gestation and found that 20% were affected by BV according to the Nugent score [7] (Table 18.1).

Common symptoms of BV include a malodorous discharge or vaginal irritation, although 50–75% of women with BV may be asymptomatic [8, 9]. The diagnosis of BV is usually based on the Amsel criteria [8] (Table 18.2). Diagnosis can be made

Table 18.1 Impact of BV treatment on PTL in low risk pregnancy

	Study subjects	Historical controls	Stats
n	2158	877	
Primiparous	49.9%	57.0%	ns
History of PTL	5.1%	4.8%	ns
BV screening	Universal	Targeted	$p < 0.01$
		1.5%	
BV treatment Mean ± SD(week)	16.4 ± 4.8(w)	20.1 ± 4.4(w)	$p < 0.05$
Total PTL	5.7%	8.6%	$p < 0.05$
Spontaneous PTL	3.1%	5.1%	$p < 0.01$
PTL <34w	0.4%	1.5%	$p < 0.01$
		Mean ± SD(week)	

Chi-square test
Unpaired t test

Table 18.2 Amsel criteria

1. Presence of thin, white, homogeneous discharge
2. An amine odor noted with addition of 10% KOH
3. Vaginal pH >4.5
4. Presence of clue cells

At least three criteria must be present

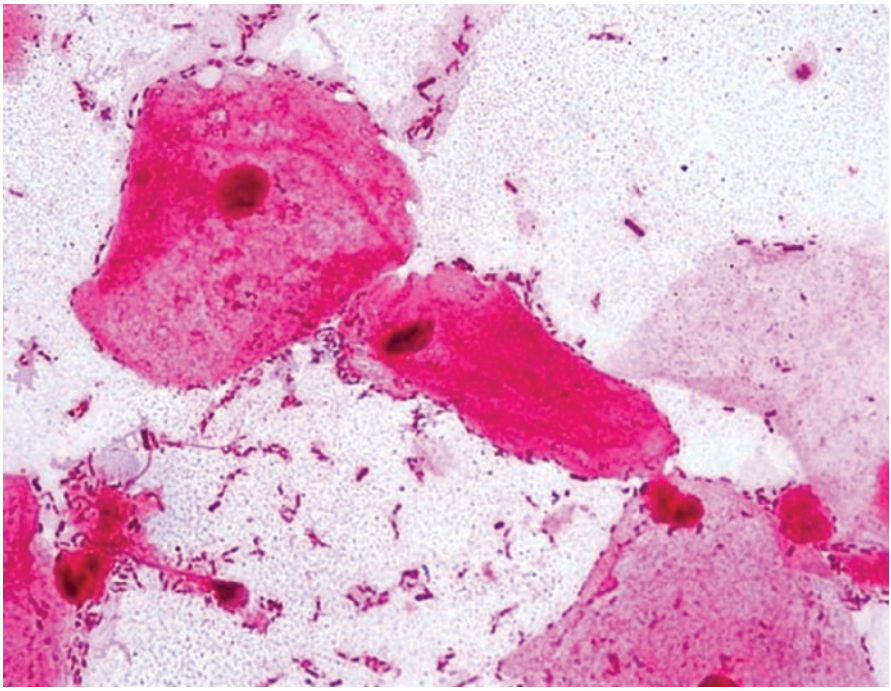

Fig. 18.1 Gram stained smear showing epithelial cells coated with bacteria

with three of the following findings [10]: (1) presence of thin, white, homogeneous discharge coating the vaginal walls; (2) an amine odor noted with the addition of 10% KOH to a sample of vaginal discharge("whiff" test); (3) vaginal pH >4.5; and (4) the presence of clue cells (Fig. 18.1) on microscopic examination. Clue cells are vaginal epithelial cells coated with adherent bacteria, which cause the edges of cells to become indistinct or stippled. The presence of more than 20% clue cells in vaginal discharge is a positive result. The first three findings are sometimes also present in patients with trichomoniasis. Gram staining with examination of bacteria in the vaginal discharge is the gold standard for diagnosis of BV, but is mostly used in research studies rather than clinical practice. The Gram stain is evaluated with the Nugent score [11]. The Nugent score is calculated from the numbers of large gram-positive rods (Lactobacillus morphotypes; weighted such that absence yielded the highest score), small gram-variable rods (G. vaginalis morphotypes; scored as 0–4), and curved gram-variable rods (Mobiluncus spp. morphotypes; scored as 0–2);

Table 18.3 Nugent score

Score	Lactobacillus morphotypes	Gardnerella and bacteroides morphotypes	Mobiluncus morphotypes
0	>30	0	0
1	5–30	<1	<1, 1–4
2	1–4	1–4	5–30, >30
3	<1	5–30	
4	0	>30	

A total score (combination of each form) of 7–10 is indicative of bacterial vaginosis infection, 4–6 is indeterminate, and 0–3 is normal

it can range from 0 to 10. A score of 0–3 is considered negative for BV, 4–6 is considered intermediate, 7 or higher is consistent with BV (Table 18.3). A high Nugent score (defined as 7–10) was strongly associated with CST IV [3].

18.3 Consequences of BV

It is known that BV is a cause of spontaneous abortion, preterm labor, preterm premature rupture of membranes, chorioamnionitis, and amniotic fluid infection [12–14]. It is caused by ascending infection to the uterus from the lower tract. In a meta-analysis of BV and preterm birth, BV increased the risk of preterm birth for single pregnant women >twofold (odds ratio [OR] 2.19, 95% CI, 1.54–3.12). In particular, risk was further increased by BV at <16 weeks of gestation (OR, 7.55; 95% CI, 1.80–31.65) or at <20 weeks of gestation (OR, 4.20; 95% CI, 2.11–8.39) [14]. In the nonpregnant state, BV is a risk factor for HIV, herpes simplex virus type 2 (HSV-2), gonorrhea, chlamydia, and trichomonas infection [15–17].

18.4 Treatment

Treatment is recommended for women with symptoms, regardless of pregnancy [10]. The recommended regimens (Table 18.4) are metronidazole 500 mg orally twice a day for 7 days; metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days; and clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days. Because oral therapy has not been shown to be superior to topical therapy for treating symptomatic BV in effecting cure or preventing adverse outcomes of pregnancy, the CDC recommends that symptomatic pregnant women can be treated with either of the same oral or vaginal regimens as nonpregnant women. Although metronidazole crosses the placenta, no evidence of a relationship between metronidazole treatment during the first trimester of pregnancy and birth defects has been found in meta-analysis [18].

Although BV has been associated with adverse pregnancy outcomes, screening and treatment of asymptomatic BV during pregnancy is controversial. A 2007 Cochrane meta-analysis [19] revealed that treatment before 20 weeks' gestation may reduce the risk of preterm birth before 37 weeks (OR 0.72, 95% CI 0.55–0.95;

Table 18.4 Treatment regimens for BV

Metronidazole 500 mg orally twice a day for 7 days OR
Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days OR
Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

five trials, 2387 women), whereas after 20 weeks, treatment did not reduce the risk of preterm birth before 37 weeks. The meta-analysis found that the detection and treatment of BV in women at high risk for preterm birth reduces the risk of preterm birth (OR 0.29, 95% CI 0.11–0.76). Takahashi et al. showed that screening and treatment before 20 weeks for low risk pregnant women reduced the risk of preterm birth before 34 weeks ($p < 0.01$) [7]. However, in a 2013 Cochrane meta-analysis [20], antibiotic treatment for BV during pregnancy was highly effective in eradicating infection, but did not significantly reduce the risk of preterm birth before 37 weeks (OR 0.88, 95% CI 0.71–1.09). Treatment before 20 weeks of gestation also did not reduce the risk of preterm birth (OR 0.85, 95% CI 0.62–1.17). In women with a previous preterm birth, treatment of BV did not affect the risk of subsequent preterm delivery (OR 0.78; 95% CI 0.42–1.48). In a different 2015 Cochrane meta-analysis [21] to evaluate the effect of prophylactic antibiotics during the second and third trimester of pregnancy, preterm delivery was reduced in the subgroup of pregnant women with a previous preterm birth who had BV during the current pregnancy (RR 0.64; 95% CI 0.47–0.88), but there was no reduction in the subgroup of pregnant women with previous preterm birth without BV during the pregnancy (RR 1.08; 95% CI 0.66–1.77). Based on these data, the American College of Obstetricians and Gynecologists, CDC, and the United States Preventive Services Task Force (USPSTF) do not recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth. The Japanese guideline [22] recommends that the screening of BV for prevention of preterm birth is performed before 20 weeks. If BV is detected, treatment is considered for managing high-risk preterm birth.

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Antenatal Corticosteroid

19

Takatsugu Maeda

Abstract

During the last 50 years, antenatal corticosteroid therapy has been valuable in patients experiencing imminent preterm birth. In recent years, its effect has been investigated and proved in detail. With a rise in the number of older patients who received antenatal corticosteroid during the early years, the attention to the long-term adverse effects is rising.

Physiological glucocorticoids (GCs) have a distinct important physiological role in accelerating development and maturation of various fetal organs in preparation for extrauterine survival. Because infants born during the early gestational age do not receive adequate exposure to GCs until birth, fetal organ maturation is delayed. This is the main mechanism for antenatal corticosteroid therapy.

Current clinical guidelines have concluded that a single course of antenatal corticosteroids should be considered routine for all imminent preterm births. On the contrary, this exposure far exceeds the physiological corticosteroid level, far before the appropriate time, so there are many concerns about its adverse effects.

We describe the physiological effects, short- and long-term effects to the infant after administration, and adverse effects of antenatal corticosteroid therapy.

Keywords

Antenatal corticosteroids · Adverse effects · Physiology

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19.1 Introduction

Since Liggins and Howie [1] published a randomized controlled trial on maternal antenatal corticosteroid administration in the early 1970s, antenatal corticosteroid administration in patients experiencing imminent preterm birth has been proven effective at reducing neonatal morbidity and mortality. In their report, the incidence of respiratory distress syndrome (RDS) in preterm infants was reduced from 15.6% to 10.0% and neonatal mortality also was reduced from 11.6% to 6.0%. Therefore, during the last 50 years, this treatment has been valuable not only in patients experiencing preterm labor but also in those requiring artificial premature birth due to maternal complications.

In contrast, infants with even a single course of antenatal corticosteroids have reduced birth weight than premature or term infants without exposure to synthetic corticosteroids. Consequently, there has been a major concern with long-term adverse effects in the recent years.

The effect of antenatal corticosteroid therapy during the periviable period of <24 weeks of gestation and the late preterm of multiple pregnancy and gestational diabetes has been inadequately evaluated.

We summarized the physiological effects of antenatal corticosteroid therapy, indications, prognosis of infants after administration, adverse effects, and future tasks.

19.2 Physiology

19.2.1 Effect of Corticosteroids

Corticosteroids are steroid hormones produced in the adrenal cortex and include glucocorticoids (GCs), cortisol, cortisone, mineralocorticoids, and aldosterone. GCs increase blood glucose levels by gluconeogenesis in the liver and suppress the inflammatory response of tissues caused by trauma, infection, and rheumatism. In addition, during physical and mental stress, secretion of adrenocorticotropic hormone (ACTH) from the pituitary is enhanced, resulting in an increase in the secretion of GCs and exerting antistress action. GCs bind to the GC receptor (GR) intracellularly and control transcription of various genes [2] (Fig. 19.1).

Physiological GC levels during pregnancy have many roles in improving the intrauterine environment. Fetal plasma GCs are primarily of maternal adrenal origin [3]. The endometrium, placenta, and fetus in the uterus are each exposed to physiological GCs arising from either maternal or fetal adrenal glands. GCs also regulate not only subsequent growth and development of the fetus and placenta but also implantation of the embryo into the uterus.

GCs have a distinctly important physiological role in accelerating development and maturation of various fetal organs, including liver, lungs, intestine, skeletal muscles, and adipose tissues, in preparation for extrauterine survival [4, 5]. The concentration of GCs in the maternal circulation continues to increase during the third trimester [5, 6]. Endogenous GC levels in fetal circulation in mice also rapidly

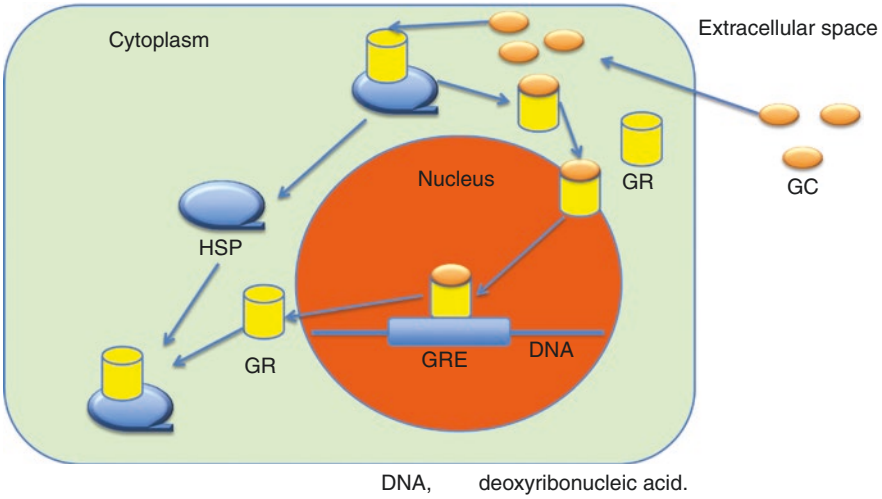

Fig. 19.1 Regulation of GC-responsive gene expression by GR. The effects of GC are mediated by GR. GR dissociates from heat shock proteins (HSP), migrates to the nucleus, and binds to GC-responsive element located in the promoter region of the target gene. This response regulates the transcriptional activity of GC-responsive genes. Then these receptors are exported to the cytoplasm and form a complex with HSP again

increase during the third trimester of pregnancy and promote development of fetal organs using the cortisol receptor, which is expressed during gestation. These physiological increases in GCs are necessary for maturation of fetal organs before birth of term infants [5, 6].

Because infants born during the early gestational age do not receive adequate exposure to GCs until birth, fetal organ maturation is delayed. This is the main mechanism for antenatal corticosteroid therapy.

In pregnant women, the placenta works as an intermediary between the mother and fetus. Maternal cortisol, which reaches the fetal circulation, is regulated by the activity of placental enzymes, which degrade endogenous GCs from the maternal circulation [6]. This regulation closely controls exposure of endogenously produced maternal GCs to the fetus. Concretely, the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD 2) is responsible for conversion of cortisol to its inactive metabolite, cortisone [6] (Fig. 19.2). This enzyme maintains a normal fetal–maternal concentration gradient of the GCs [7]. Exposure of the fetus to the mother's GCs can be presumed to depend at least partly on the placental activity of this enzyme. A decrease in the placental expression of 11β-HSD 2 occurs at approximately 38–40 weeks of gestation and allows maternal cortisol to enter the fetal circulation during late pregnancy [8]. The proper timing of this event is important, as the fetal organs eventually mature to prepare for extrauterine survival.

Maternal malnutrition causes a decrease in birth weight of the fetus and placental weight accompanied with an increase in maternal plasma GCs and decrease in placental expression of 11β-HSD 2 overexposed to maternal corticosterone in rats [9]. Fetal overexposure to endogenous maternal GCs, such as maternal psychological

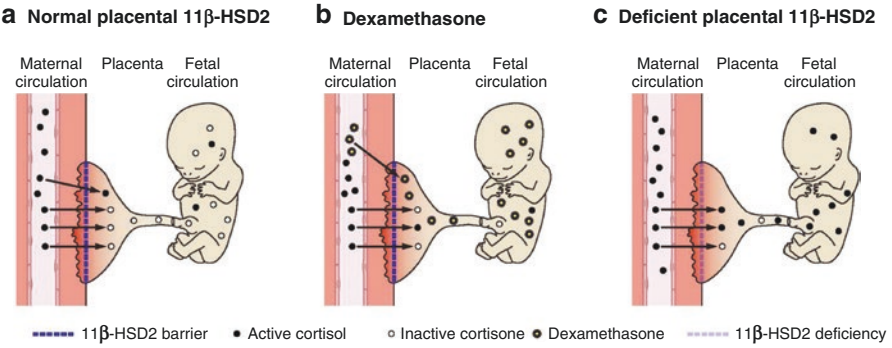

Fig. 19.2 GC programming and placental 11β-HSD2. Placental 11β-HSD2 debulks the much higher levels of active GCs in the maternal blood. (**a**) Normally, the enzyme oxidizes cortisol to inert cortisone that cannot be regenerated in the fetus, which lacks 11β-HSD1 until near term. Thus, the major source of active cortisol in the fetus is its own adrenal glands. (**b**) Maternal treatment with dexamethasone, which is a poor substrate for 11β-HSD2 and, thus, passes the placenta intact, increasing GC action on the fetus and placenta, reducing growth, and altering the developmental trajectory of specific tissues. (**c**) Similarly, inhibition or relative deficiency of placental 11β-HSD2 allows increased passage of active maternal GCs to the fetus and placental receptors. Lowering of placental 11β-HSD2 occurs with genetic mutations, consumption of licorice, maternal malnutrition, infection, or stress. This figure is reproduced from Chapman K, Holmes M, Seckl J. 11β-hydroxysteroid dehydrogenases: intracellular gatekeepers of tissue glucocorticoid action. Physiol Rev. 2013;93:1139–206

stress, results in a programmed increase in body mass index and body fat percentage, insulin resistance, and atherogenic lipid profile at adulthood in humans. Low-protein diet in pregnant maternal animals, studied as an experimental model of programming of the metabolic syndrome, has been associated with changes in deoxyribonucleic acid (DNA) methylation in key genes [10]. Maternal low-protein diets resulted in GR overexpression and decreased expression of 11β-HSD 2 in the fetal liver, lungs, kidneys, and brain [11]. The animal models of disease programming, human studies, and epidemiological data have shown that GCs have an important role in the development of adult cardiometabolic diseases and neonatal psychological diseases.

The two most common synthetic GCs administered to pregnant women are the fluorinated corticosteroids, betamethasone and dexamethasone. They generally are preferred for use in antenatal treatment to accelerate fetal organ maturation. Both pass through the placenta in their active form and have nearly identical biological activity. Antenatal corticosteroid therapy in mice can induce stability and maturation of the capillaries of the choroid plexus by increasing the thickness and integrity of the basement membrane and reduce the incidence of paraventricular and intraventricular hemorrhage [12]. On the contrary, they are resistant to metabolism by 11β-HSD 2 (Fig. 19.2). With synthetic GC exposure, this enzyme is bypassed and direct exposure to the fetus occurs. The deleterious effect of GCs can be expressed directly by maternal synthetic GC administration and stress-induced endogenous maternal GC oversecretion or indirectly through other types of stress, such as food restriction.

19.3 Indications

According to current clinical guidelines, pregnant women at risk for preterm delivery before 37 weeks of gestation have been proved to be candidates for antenatal corticosteroid treatment [13]. Antenatal corticosteroid administration should not be altered by fetal race, sex, or the feasibility of surfactant replacement therapy [14]. Administration of antenatal corticosteroids to women at risk for premature birth is associated strongly with a reduction in neonatal morbidity and mortality [4]. A single course of corticosteroids is recommended for pregnant women at risk for premature birth within 7 days, between 24 and 34 weeks of gestation, and may be considered for pregnant women at 23 or more weeks of gestation [15]. A Cochran meta-analysis proved the beneficial effects of this therapy regardless of the membrane status and supported the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation [16].

19.3.1 Imminent Preterm Birth

All fetuses between 24 and 36 weeks of gestation at risk for preterm birth should be considered candidates for prenatal treatment with corticosteroids. Patients who are indicated for administration of tocolytic agents also should be indicated for treatment with antenatal corticosteroids [14]. The recommended course of treatment includes administration of 12-mg betamethasone intramuscularly twice at 24-h intervals or four doses of 6-mg dexamethasone every 12 h [13–16]. This treatment is not standardized in some countries, and it is possible to administer multiple courses [17]. However, it has been suggested that multiple courses of corticosteroid administration do not significantly improve clinical prognosis [15, 18]. Antenatal corticosteroid therapy remains standard therapy in the antenatal prevention of intraventricular hemorrhage (IVH), RDS, and necrotizing enterocolitis (NEC) [19]. In fact, a single course of antenatal corticosteroid therapy improved most neurodevelopmental prognoses in preterm infants born before 34 weeks of gestation [20]. Even preterm births of <24 h after corticosteroid administration are associated with a significant reduction in neonatal morbidity and mortality. Therefore, corticosteroid administration is recommended even when the possibility of a second administration is low [13, 21].

A final additional consideration on the risk of antenatal corticosteroid administration is that antenatal corticosteroids are not contraindicated, even in the case of sepsis [22, 23].

19.3.2 Preterm Rupture of Membranes

Antenatal corticosteroid administration after preterm rupture of membranes (PROM) has been shown to reduce neonatal mortality, RDS, IVH, and NEC. Recent data indicated that antenatal corticosteroid administration is not associated with an

increased risk of maternal infection or neonatal infection regardless of gestational weeks [16, 24–26]. A single course of corticosteroid administration is recommended for preterm pregnant women with PROM between 24 0/7 and 33 6/7 weeks of gestation. In addition, regardless of the status of the membrane, pregnant women who are at risk for premature delivery within 7 days of pregnancy over 23 0/7 weeks can be considered for antenatal corticosteroids [13, 16, 22]. Whether to conduct a repeat or rescue course of antenatal corticosteroids in patients with preterm PROM is controversial, and there is insufficient evidence to recommend or oppose this therapy.

19.3.3 Multiple Pregnancies

Clinical trials have been performed to confirm the benefits of a single course of antenatal corticosteroid therapy for multiple fetuses. More recently, in a well-designed retrospective cohort study, antenatal GC therapy in twin pregnancies 1–7 days before birth was associated with a significant decrease in preterm neonatal mortality, short-term respiratory morbidity, and severe neurological injury, which was observed similarly in singleton pregnancies [27]. In addition, very low birth weight multiple gestation infants exposed to antenatal corticosteroids might respond similarly to a singleton, but it was not clear if the delivery occurred due to inappropriate timing [28]. A Cochrane database review concluded that antenatal corticosteroids are beneficial in single pregnancies, but further research is needed to demonstrate the improvement in outcomes of multiple pregnancies [16, 29]. Unless contraindication exists, all pregnant women at risk for delivery within 7 days from 24 0/7 to 33 6/7 weeks should be administered antenatal corticosteroids, regardless of the fetal number [14, 29]. In addition, regardless of the fetal number, antenatal corticosteroid administration may be considered if pregnant women who are starting therapy at 23 0/7 weeks are at risk for preterm birth within 7 days [15].

19.3.4 Late Preterm

Regarding antenatal corticosteroid administration at 34–36 weeks of gestation, a randomized controlled trial (RCT) reported that this therapy decreased neonatal respiratory disorders. Based on this report, the American Congress of Obstetricians and Gynecologists (ACOG) gave notice of the change recommended for antenatal corticosteroid administration in this period as a Committee Opinion in 2017 [15]. Administration of betamethasone can be considered in pregnant women between 34 0/7 and 36 6/7 weeks of gestation at risk for preterm birth within 7 days and who have not received antenatal corticosteroids previously [15].

In an antenatal steroid administration study of the maternal fetal medical unit (MFMU) network, a double-blind, placebo-controlled RCT was conducted to evaluate the use of betamethasone in pregnant women at high risk for preterm birth in the late preterm of pregnancy [30]. A high risk pregnant woman was identified if preterm birth was imminent, she had preterm PROM, or an obstetrician/gynecologist

scheduled an artificial premature birth. Tocolysis was not used as a part of this study and delivery was not delayed due to obstetric or medical indications. This study found that administration of betamethasone resulted in a significant reduction in the need for respiratory support as the primary outcome. Severe respiratory complications largely decreased from 12.1% in the placebo group to 8.1% in the betamethasone group (relative risk [RR], 0.67; 95% confidence interval [CI], 0.53–0.84; $P < 0.001$). The frequency of newborn transient hyperventilation, RDS complex bronchopulmonary dysplasia, RDS transient hyperventilation, and RDS, and the cases requiring surfactant replacement also were significantly reduced. Infants exposed to betamethasone were less likely to require resuscitation immediately after birth. Women in the late preterm, diagnosed with clinical chorioamnionitis (intrauterine infection), are not indicated for antenatal corticosteroid administration.

Further, tocolysis should not be used in an attempt to delay delivery to administer antenatal corticosteroids in the late preterm, and women with late preterm births due to maternal indications [31].

Groups that have not been researched for late preterm steroid administration include multiple pregnant women, those with pregestational diabetes, pregnant women who received a course of corticosteroids previously, and women who delivered by cesarean section at term. Whether antenatal corticosteroids provided benefit in the late preterm in these populations is unknown [15].

19.3.5 Periviable Period

Although large-scale observational studies have shown the effectiveness of antenatal corticosteroid administration at 22–23 weeks of gestation, the evidence remains inadequate [32]. A recent study published from Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) neonatal research network revealed a decrease in mortality and neurodevelopmental impairment at 23 (83.4% vs. 90.5%), 24 (68.4% vs. 80.3%), and 25 (52.7% vs. 67.9%) weeks of gestation [16, 22, 33]. In this study, antenatal corticosteroid administration also reduced the incidence of IVH, periventricular leukomalacia (PVL), and NEC in infants born at 23 0/7 to 25 0/7 weeks of gestation. This evidence suggested that antenatal corticosteroid therapy is most beneficial for infants at the limits of viability [33]. On the contrary, there was no significant difference in these prognoses among infants born at 22 0/7 through 22 6/7 weeks of gestation (90.2% vs. 93.1%). In addition, RDS risk increased in neonates with earlier gestational age, which was independent of whether the course of antenatal corticosteroid therapy was achieved, and infants might be exposed unnecessarily to potent therapeutic agents. There was no remarkable advantage for antenatal corticosteroid therapy when administered before 23 weeks of gestation [33].

Conversely, the Neonatal Research Network of Japan reported that antenatal corticosteroid exposure was associated with a significant decrease in mortality of preterm infants born at 22 or 23 weeks of gestation (adjusted hazard ratio [HR], 0.72; 95% CI, 0.53–0.97), decrease in IVH (odds ratio [OR], 0.49; 95% CI, 0.36–0.67),

severe IVH (OR, 0.64; 95% CI, 0.51–0.79), and decrease in mortality (adjusted HR, 0.65; 95% CI, 0.50–0.86) [34].

Because of detrimental adverse developmental effects, it is important to consider whether the benefit is more important than the risk. However, even in a pregnant woman who is at risk for preterm birth within 7 days after 23 0/7 weeks of gestation, ACOG stated that it is possible to consider administering antenatal GCs to those with PROM and multiple pregnancies if families desire resuscitation [15].

19.4 Prognosis

Roberts et al. [16] conducted a systematic review of 30 studies on prenatal steroid administration to pregnant women with imminent premature birth in 2017. Treatment with antenatal corticosteroids (compared to placebo or no treatment) was associated with a reduction in the most serious adverse outcomes related to prematurity, including perinatal death (average RR, 0.72; 95% CI, 0.58–0.89), neonatal death (RR, 0.69; 95% CI, 0.59–0.81), RDS (average RR, 0.66; 95% CI, 0.56–0.77), moderate/severe RDS (average RR, 0.59; 95% CI, 0.38–0.91), IVH (average RR, 0.55; 95% CI, 0.40–0.76), NEC (RR, 0.50; 95% CI, 0.32–0.78), need for mechanical ventilation (RR, 0.68; 95% CI, 0.56–0.84), and systemic infections in the first 48 hours of life (RR, 0.60; 95% CI, 0.41–0.88). There was no obvious benefit for chronic lung disease (average RR, 0.86; 95% CI, 0.42–1.79), mean birth weight (g) (mean difference [MD], −18.47; 95% CI, −40.83 to 3.90), death in childhood (RR, 0.68; 95% CI, 0.36–1.27), neurodevelopment delay in childhood (RR, 0.64; 95% CI, 0.14–2.98), or death into adulthood (RR, 1.00; 95% CI, 0.56–1.81). Treatment with antenatal corticosteroids did not increase the risk of chorioamnionitis (RR, 0.83; 95% CI, 0.66–1.06) or endometritis (RR, 1.20; 95% CI, 0.87–1.63). No increased risk in maternal death was observed [16].

19.5 Adverse Effects

19.5.1 Maternal Adverse Effects

An increasing risk of maternal infection and suppression of the hypothalamic–pituitary–adrenal system are concerning maternal adverse effects with antenatal corticosteroid administration [15]. However, the ACOG concluded that antenatal corticosteroid administrations are not contraindicated even for pregnant women with sepsis [13, 15].

19.5.2 Infantile Adverse Effects

It is conceivable that exposure to synthetic corticosteroids in the uterus at a critical developmental stage may change the function of many organ systems extending to

adulthood. Although antenatal corticosteroid therapy has been proven to be clinically effective for prevention of IVH, RDS, and NEC, it also may cause adverse effects [35]. In a review in 2014, infants with even a single course of antenatal corticosteroids had an 18% reduction in birth weight, 9% decrease in head circumference, and 6% decrease in height, and the incidence of placental anomalies was increased compared to premature or term infants without exposure to synthetic corticosteroids [36].

Although adverse side effects were observed after multiple courses of antenatal and postnatal corticosteroid therapy, it is widely accepted that single course corticosteroid therapy has no significant adverse effects. While the NICHD 2000 Consensus Panel reported the possibility of the benefit of repeated course administration (especially in the reduction of severity of respiratory distress), it has been emphasized from animals and human data that there also are adverse effects for fetal cerebral myelination, lung growth, and hypothalamic–pituitary–adrenal function [36]. Although not consistent, the results of six studies revealed a decrease in birth weight and head circumference with repeated courses and three studies did not.

The concerns that corticosteroids can adversely affect the prognosis of neurodevelopment are based primarily on animal data and studies with multiple courses of corticosteroid administration. The MFMU study suggested that four or more repeated courses of corticosteroids may be associated with development of cerebral palsy [37]. In fact, the Multiple Courses of Antenatal Corticosteroids for preterm birth study at 5 years of age (MACS-5) noted that multiple courses of antenatal corticosteroids might increase the risk of neurodevelopment and neuropsychosis at the age of 5 years [18].

Furthermore, what is relevant is a particular outcome based on the timing of antenatal corticosteroid administration before delivery. This is true particularly for infants with long-term intrauterine exposure who were not delivered during premature birth. What is of concern is that approximately 70% of pregnant women who received antenatal corticosteroids because of imminent preterm birth were not going to deliver within 7 days, the accepted time of maximum benefit [38]. While the maximum effect occurs from 24 h to 7 days after antenatal corticosteroids, it is not clear whether longer term exposure to the corticosteroids in utero enhances or reduces the effects of adverse neurodevelopment [36]. Additionally, the long-term effects of corticosteroid exposure at different developmental stages of fetal growth are not well understood.

Other side effects of multiple course antenatal corticosteroid administration include elevated risk of chorioamnionitis [39]. The monitoring of long-term prognosis after intrauterine steroid exposure should be continued.

19.6 Optimization

Although antenatal corticosteroid therapy is administered routinely, the complete effect is not always obtained. To implement optimal antenatal corticosteroid therapy, individualized therapy in the clinical setting is necessary. Specifically, factors

that may influence the response to antenatal corticosteroid therapy include sex, race, and birth weight [40–42]. It is essential to understand the variables that affect the response to antenatal corticosteroid therapy to improve clinical prognosis.

19.6.1 Fetal Sex

Many studies report different clinical outcomes of antenatal corticosteroid therapy based on fetal sex. A particular study examined very low birth weight (VLBW) infants and found that "VLBW male newborns (compared to girls) are at a higher risk for development of IVH and severe IVH but not PVL" [43]. Lim et al. [44] confirmed that male sex in VLBW infants was associated with worsening outcomes in specific research populations.

19.6.2 Maternal Ethnicity

A study to evaluate the influence of maternal ethnicity also has been reported and the ethnicity of pregnant women is "independently associated with neonatal respiratory prognosis" after antenatal corticosteroid therapy [41]. Also, according to a recent report, adjustment of gestational age and birth size has shown that Caucasian infants have a significantly higher incidence of RDS than non-Caucasian infants [45].

19.6.3 Birth Weight (Intrauterine Growth-Restricted Fetus)

Clinical data suggest that the effect of antenatal corticosteroid therapy in fetal growth restriction (FGR) is limited and whether antenatal corticosteroid therapy is beneficial is unknown [46]. In a recent study regarding antenatal corticosteroid therapy for an infant with a birth weight of less than 1500 g (FGR), there were no significant differences between exposed and unexposed infants with short- or long-term fetal benefits. This suggested that antenatal corticosteroids may not be beneficial to all populations of preterm birth infants [40]. In fact, RDS risk increases in lower gestational age infants, which is independent of whether the completed course of antenatal corticosteroid therapy has been achieved and these infants can be exposed to unnecessarily potent therapeutic agents. When administered before 23 weeks of pregnancy, there is no significant benefit for antenatal corticosteroid therapy [33].

19.6.4 Type of Corticosteroids

There are 12 trials comparing dexamethasone and betamethasone in Cochran meta-analysis [5]. Dexamethasone was associated with a reduced risk of IVH compared to betamethasone (RR, 0.44; 95% CI, 0.21–0.92). No statistically significant

differences were seen for incidence of RDS (RR, 1.06; 95% CI, 0.88–1.27), perinatal death (neonatal death RR, 1.41; 95% CI, 0.54–3.67), Apgar score less than seven at 5 min (RR, 0.97; 95% CI, 0.43–2.18); Apgar score at 5 min (MD, 0.23; 95% CI, −0.23 to 0.70), mean birth weight (MD, 0.01 kg; 95% CI, −0.11 to 0.12), low birth weight less than 2500 g (RR, 0.89; 95% CI, 0.65–1.24), head circumference (MD, 50 cm; 95% CI, −1.55 to 0.55), vasopressor use (RR, 0.44; 95% CI, 0.17–1.11), bronchopulmonary dysplasia (RR, 2.50; 95% CI, 0.10–61.34), severe IVH (RR, 0.40; 95% CI, 0.13–1.24), PVL (RR, 0.83; 95% CI, 0.23–3.03), neonatal sepsis (RR, 1.30; 95% CI, 0.78–2.19), NEC (RR, 1.29; 95% CI, 0.38–4.40), retinopathy of prematurity (RR, 0.93; 95% CI, 0.59–1.47), and patent ductus arteriosus (RR, 1.19; 95% CI, 0.56–2.49). Similarly, very few differences were seen for rate of admission to the neonatal intensive care unit (NICU), although in one trial, those infants exposed to dexamethasone, compared to betamethasone, had a significantly shorter length of NICU admission (MD, −0.91 days; 95% CI, −1.77 to −0.05). Compared to intramuscular dexamethasone, oral dexamethasone significantly increased the incidence of neonatal sepsis (RR, 8.48; 95% CI, 1.11–64.93) in one trial of 183 infants. No statistically significant differences were seen for other outcomes reported. Apart from a reduced maternal postpartum length of stay for women who received betamethasone at 12- compared to 24-h intervals in one trial (MD, −0.73 days; 95% CI, −1.28 to −0.18; 215 women), no differences in maternal or neonatal outcomes were seen between the different betamethasone dosing intervals assessed. Similarly, no significant differences in outcomes were seen when betamethasone acetate and phosphate were compared to betamethasone phosphate in one trial [4].

19.6.5 Dose

It is difficult to find a high-quality study that compared the dose, administration interval, and administration route. ACOG recommended that treatment should consist of either two 12-mg doses of betamethasone given intramuscularly 24 h apart or four 6-mg doses of dexamethasone administered intramuscularly every 12 h [13, 15].

19.6.6 Number of Courses

The benefit of corticosteroid administration is greatest at 2–7 days after initial administration [16]. It is unknown whether repeated doses of antenatal corticosteroids are beneficial. Therefore, regularly scheduled repeat courses and continuous courses (more than two courses) currently are not recommended [13, 15].

The concerns that corticosteroids can adversely affect the outcome of neurodevelopment are based largely on animal data and studies with multiple courses of corticosteroid administration [37]. It is well known that corticosteroids inhibit cell expansion and DNA replication. Studies of small and large animals have shown that

exogenous steroids suppress fetal growth and increase fetal blood pressure [47, 48]. In sheep, lambs exposed to up to four doses of betamethasone administered to the ewe have a dose-dependent decrease in birth weight, but exogenous steroids administered directly to the fetus do not inhibit fetal growth [49, 50]. Other animal studies have shown that repeated administration of corticosteroids has a detrimental effect on neuron myelination and the development of new interalveolar septa, such as emphysematous and hypothalamic–pituitary–adrenal (HPA) function [49, 51, 52]. The impact on the HPA axis may persist into adulthood.

In humans, similar concerns occur from nonrandomized cohort studies with adverse effects after repeated administrations of corticosteroids on birth size, risk of neonatal infection, fetal pituitary–adrenal axis function, and neonatal blood pressure [53–55]. Long-term follow-up surveillance of infants exposed to repeated administration of antenatal corticosteroids has been limited to date and creates conflicting results. Nonrandomized trials have shown developmental delay and adverse effects on childhood behavior, but in other nonrandomized studies, there was no difference between exposed and unexposed children, or there was a possibility that cerebral palsy had decreased [54–59].

Other long-term adverse effects due to single or repeated doses of antenatal corticosteroids may program the fetal cardiovascular setting and lead to adult hypertension, and may cause insulin resistance leading to diabetes [60, 61]. Increased exposure of the fetus to GCs has been suspected to be associated with decreased birth weight and association with adult cardiovascular and metabolic diseases [62]. Therefore, uncertainty remains whether there is a benefit to repeating the dose of antenatal corticosteroids in women at risk for preterm birth in an initial course. The currently available evidence reveals it does not cause serious harm in early childhood, but it does not result in benefit.

19.6.7 Rescue Dose

Peltoniemi et al. [63, 64] researched whether rescue courses (12-mg betamethasone) in pregnant women with imminent preterm labor more than 1 week after administration of antenatal corticosteroids (when delivery within 48 h is expected) can improve fetal prognosis. There was no significant difference in neonatal mortality (RR, 2.90; 95% CI, 0.75–1.12), RDS (RR, 1.16; 95% CI, 0.75–1.79), severe RDS (RR, 1.40; 95% CI, 0.90–2.19), and severe IVH (RR, 1.58; 95% CI, 0.44–5.71) between the betamethasone rescue courses and placebo groups, but there was a tendency for more high frequency in the rescue courses group, and this study was canceled halfway due to safety consideration [63]. Also, there were no significant differences between the two groups in long-term neurological prognosis, height, weight, and head circumference at 2 years of age [64].

Recently, however, ACOG recommended that a pregnant woman who already had received antenatal corticosteroids more than 14 days previously and who was before 34 weeks of gestation with a risk of preterm birth within 7 days should be considered for additional steroid administration [13, 15].

Whether to administer the rescue course of corticosteroids to patients with PROM during the premature stage is controversial and there is inadequate evidence to recommended therapy or not [24, 65].

19.6.8 Timing of Administrations

Although not well studied, the timing of corticosteroid therapy before delivery is likely to affect clinical outcomes. The optimal therapeutic window for delivery after antenatal corticosteroid administration is 2–7 days. One study reported that women who deliver preterm in that window constituted only 20–40% of preterm births at their institution [66]. The Ohio Perinatal Quality Collaborative reported that the rate of antenatal corticosteroids had increased and was maintained at a high level when the hospital recognized that the use of prenatal corticosteroids was being monitored [67]. Improvements to optimize appropriate, timely, antenatal corticosteroid administration currently are being investigated.

19.7 Conclusion

Antenatal corticosteroid therapy is a powerful and an effective treatment method. On the contrary, there are several concerns regarding the adverse effects of fetal high dose and early fetal gestational age exposure to synthetic corticosteroid. Long-term follow-up on side effects while administering appropriate corticosteroid therapy is considered indispensable in the future.

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Preterm Birth and Mode of Delivery

20

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Abstract

Most previous studies regarding the mode of delivery in preterm birth have shown no difference in maternal and neonatal outcomes based on the intended mode of delivery. The mode of delivery of preterm delivery is problematic because that sufficient data from prospective randomized trials are not available at present, while recommendations for clinical practice were taken from a retrospective study. Therefore, the optimal delivery method for preterm infants has not yet been concluded. Based on the available limited evidence in this review, in the case of intended preterm delivery, vaginal delivery and/or induction of labor should be considered when early preterm birth is indicated as far as the fetus is reassuring with vertex presentation. However, in cases of breech presentation and/or multifetal pregnancy, cesarean delivery might be considered if they are viable at a more advanced gestational age.

Keywords

Preterm birth · Mode of delivery · Breech presentation · Multifetal pregnancy · Cesarean delivery

20.1 Introduction

Primarily maternal and neonatal outcomes relating to the mode of delivery have been studied in term deliveries, and it is established that vaginal delivery at term provides maternal and neonatal benefits. When preterm birth is indicated, physicians usually

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prefer a planned cesarean delivery rather than induction of labor because of a prolonged induction, an unfavorable cervix, or concern for fetal intolerance of labor. In this context, preterm cesarean delivery rate continues to rise to 46.6% in 2013 [1]. The survival rate of premature infants has improved remarkably because of the use of antenatal steroids, advances in assisted ventilation, and surfactant therapy. They resulted in a marked decline in neonatal mobility and mortality in the past two decades, especially the mortality in 23–24 weeks and also in the morbidity 25–28 weeks gestation [2]. In contrast, intraventricular hemorrhage (IVH) is usually affected in 23–25% of very low birth weight infants, which is not only the cause of cerebral palsy and neurodevelopmental delay but also of neonatal mortality [3, 4]. In this regard, it is becoming essential to reduce the incidence of IVH for better neonatal outcomes in preterm birth, while there is still no consensus about whether cesarean delivery is beneficial to reduce the perinatal risks such as intraventricular hemorrhage (IVH) or perinatal death.

20.2 Mode of Delivery of the Preterm Infants

At present, none of the existing guidelines explicitly discuss the mode of delivery of extremely premature infants. In Cochrane review for preterm birth in singletons with either cephalic or breech presentation concluded that evidence was not enough to evaluate the use of a policy of planned immediate cesarean delivery for preterm babies [5]. In this field, the problem is the difficulty of recruitment of patients and randomization. As the Cochrane review of randomized trials about preterm delivery reported on 116 women only, knowledge on the effectiveness of cesarean section and vaginal delivery was obtained from non-randomized studies. The NICE guideline recommended that cesarean section is preferably for women with the breech presentation between 26 and 36 weeks, while no recommendations for pregnant women <26 weeks gestation because of limited evidence [6].

20.2.1 Preterm Birth and Singleton

A population-based cohort study was done by the German Neonatal Network (GNN) [7]. A total cohort of 2203 singleton, very low birth weight infants (<1500 g) whose gestational age ranges from 22 to 36 weeks were enrolled. Of 2203 infants, the prevalence of IVH was more frequent in the vaginal delivery (26.6%) and by emergency cesarean section (31.1%), as compared to planned cesarean section (17.2%), respectively. Elective cesarean section can reduce the risk of IVH in preterm infants <30 weeks' gestation when presenting with preterm labor regardless of its presentation.

In 2006, a prospective cohort study was conducted in England, which enrolled 1722 cases of singleton delivered at 22–26 weeks' gestation. They investigated the effect of delivery mode on birth in good condition (infant heart rate >100 at 5 min of age) and delivery-room death [8]. Cesarean delivery at <26 weeks' gestation was

associated with improved condition at birth and lower odds of delivery-room death, whereas there was no association in neonates delivered at 26 weeks or later with spontaneous labor. There was a strong association between antenatal steroids and improvement of outcomes in neonates delivered vaginally.

A retrospective cohort study was conducted examining New York City birth data between 1995 and 2003 [9]. This study included singleton, live born, vertex neonates delivered between 25 and 34 weeks. Of 20,231 neonates, 69.3% were delivered vaginally, and 30.7% were delivered cesarean. Cesarean delivery showed no protection against poor outcomes between 24 and 34 weeks and was associated with increased risk of respiratory distress and low Apgar score compared with vaginal delivery.

Durie and colleagues studied neonatal outcomes according to the delivery mode in preterm infants with vertex presentation (weighing <1500 g) [10]. There was no increase in odds of death, severe IVH, necrotizing enterocolitis, or sepsis in the vaginal delivery group compared with the cesarean group.

Anderson and colleagues performed an interesting study regarding the role of cesarean delivery in IVH prevention in low birth weight infant (≤1750 g) [11]. Intracranial hemorrhage was confirmed in 31.5% of infants within 1 h after birth, while in additional 17% of the infants beyond 1 h after birth. Infants with intracranial hemorrhage had a significantly lower gestational age and birth weight. Of note, intracranial hemorrhage within 1 h after delivery and progression to grades III and IV hemorrhage were more common in the infants of women who had the active phase of labor regardless of the route of delivery.

In 2013, a retrospective cohort study was done among 158 vertex deliveries (22 and 29 weeks and/or weighing <1500 g) [12]. Mild IVH increased in those exposed to the second stage of labor, although no clear association was seen between the duration of second stage and incidence of IVH. Although in clinical practice, there is no reality to avoid active-phase labor in preterm birth because clinicians usually make clinical decisions after confirmation of the progress of labor and painful contractions.

20.2.2 Preterm Birth and Singleton with Breech Presentation

Cesarean section is the safest mode of delivery at term with breech presentation, with three times lower risk of death or serious mobility than vaginal birth [13]. Breech presentation is more frequent in early gestation, observed in 30–35% of fetuses at 22–28 weeks' gestation, while this percentage falls to 4% in term pregnancy [14, 15]. In preterm infants with breech presentation, the preferred mode of delivery in relation to neonatal outcome is still controversial.

Regarding preterm birth with the breech presentation, a systematic review of nonrandomized studies has performed and determined the association between mode of delivery and neonatal mortality at 25–36 weeks' gestation [16]. Seven studies, a total of 3357 women were involved in this review. The weighted risk of neonatal mortality was lower in the cesarean section group compared to the vaginal delivery group

(3.8% versus 11.5%). The pooled analysis showed that cesarean section reduced the risk of neonatal mortality by 37%. Kayem and colleagues compared neonatal morbidity and mortality rates in preterm breech deliveries at 26–29 weeks' gestation with a policy of either planned vaginal delivery or planned cesarean delivery [17]. The risks of mortality and severe morbidity in preterm breech were not increased by vaginal delivery. Three neonates (1.7%) died from head entrapment after vaginal delivery in the planned vaginal delivery group. They concluded that such cases were possible in case of vaginal delivery, but its rarity should be balanced with the maternal consequences of early preterm cesarean delivery.

A retrospective cohort study was conducted in singleton preterm births at 23–34 weeks' gestation, which included malpositioned fetus [18]. Labor was induced in 331 patients, of whom 208 (63%) delivered vaginally and maternal and neonatal outcomes did not differ based on the intended mode of delivery.

In 2017, a meta-analysis was undertaken to determine the safest delivery mode in extremely preterm breech singletons at 23–27 weeks' gestation, who were actively resuscitated after birth [19]. They included 15 studies with 12,335 infants. Cesarean section was associated with a 41% decrease in odds of death (odds ratio (OR) 0.59, 95% confidence interval (CI) 0.36–0.95), with the greatest decrease at 23–24 weeks' gestation and also associated with a 49% decrease in odds of severe IVH (OR 0.51, 95% CI 0.29–0.91) in breech singletons <28 weeks' gestation.

Based on the above results, the cesarean section could reduce the neonatal risk of both death and IVH for the fetus with breech presentation, especially in extremely preterm birth (less than 28 weeks). Therefore, at present, the cesarean section is applied for preterm breech presentation in most developed countries.

20.2.3 Preterm Delivery with Multifetal Pregnancy

The incidence of twin pregnancy has increased worldwide over the last 30 years mainly because of the assisted reproductive technology, which results in approximately one-third of very preterm birth (<32 weeks' gestation) [20]. In the USA, the twinning rate rose 76% from 1980 to 2009 and was generally stable for 2009–2012 [21]. The triplet and higher-order multiple birth rose more than 400% from 1980 to 1998, but has decreased to 48% since the 1998 peak [21]. In routine obstetric practice, twin delivery remains a challenging event even more in preterm birth. Problems with the first twin presenting as a breech are similar to those encountered of a singleton breech fetus.

In 2005, a retrospective cohort study of all twin births in Scotland between 1985 and 2001 was conducted. They determined the risk of perinatal death among twins born at or after 36 weeks of gestation in relation to mode of delivery [22]. Of 8073 births, there were six deaths of the first twins and 30 deaths of the second twins (odds ratio (OR) for second twin 5.00, 95% CI 2.00–14.70). They concluded that a planned cesarean section may reduce the risk of perinatal death of twins at term by approximately 75% compared with attempting a vaginal birth.

Barzilay and colleagues conducted a retrospective cohort study of twin pregnancies in which the second twin's birth weight was ≤1500 g [23]. Trial of vaginal delivery was successful for both twins in 90.5% of cephalic–cephalic twins and 96.4% in cephalic–noncephalic twins, while the rate of IVH (grade 3–4) was significantly higher in the vaginal delivery group. They suggested vaginal delivery of very low birth weight twins is associated with an increased risk of IVH, regardless of presentation.

A retrospective multicenter study was performed to assess the neonatal mortality and morbidity in very preterm twins between 26 and 31 weeks' gestation with the first twin in cephalic presentation [24]. Twins delivered after preterm labor and/or preterm rupture of membranes are classified into two groups according to the management policy: a policy of planned vaginal delivery and a policy of planned cesarean delivery. Planned vaginal delivery had no independent effect on neonatal mortality in a hospital or severe neonatal composite morbidity. A policy of planned vaginal delivery of very preterm twins with the first twin in cephalic presentation does not increase either severe neonatal morbidity or mortality.

Regarding preterm delivery of triplets or higher-order gestation, monitoring of fetal heart rate during labor is difficult. Moreover, cord prolapse, malposition of subsequent fetuses, bleeding from separating placenta could occur after the first neonate is delivered. For these reasons, many clinicians perform a cesarean section.

In the USA, the risks of stillbirth and neonatal and infant death were studied in triplets delivered at ≥24 weeks' gestation between 1995 and 1998 [25]. Cesarean delivery of all triplet fetuses is associated with the lowest neonatal and infant mortality rate; hence, they recommend to avoid vaginal delivery. Lappen and colleagues assessed maternal and neonatal outcomes of attempted vaginal versus planned cesarean delivery in a retrospective cohort study [26]. Triplet at a gestational age ≥28 weeks was enrolled. Twenty-four sets of triplets had an attempted vaginal delivery and are associated with higher risks of maternal transfusion and neonatal mechanical ventilation. They recommend to prelabor cesarean delivery for triplets.

As for the delivery route for a twin pregnancy, if the first twin presenting as a breech should be performed a cesarean delivery. A trial of labor is reasonable in women with a cephalic–cephalic presentation. Concern to the optimal delivery route for cephalic–noncephalic twin pairs remains controversial. Based on the retrospective, large population-based studies, cesarean delivery is appropriate because it may decrease mobility in preterm second twins. In preterm delivery of triplets or higher-order gestation, cesarean delivery is necessary.

20.2.4 Preterm Delivery and Preeclampsia

Preeclampsia is one of the major indications for preterm birth, whereas evidence of the optimal mode of delivery is lacking. Alexander and coworkers performed a retrospective study in pregnancies complicated by severe preeclampsia to compare the effects of labor induction cesarean delivery without labor in very low birth weight infants (750–1500 g) [27]. Vaginal delivery was accomplished by 50 (34%) women in the induction group. Apgar score of 3 or less at 5 min was more frequent in the

induced-labor group (6% versus 2%), but other neonatal outcomes were not different such as neonatal death, intraventricular hemorrhage. In 2019, a retrospective study was conducted to investigate labor success rates of the intended mode of delivery between 24 and 33 weeks and compare maternal and neonatal outcomes [28]. Among the 460 women with induction (50%), 47% of them delivered vaginally. The success rate of vaginal delivery increases as progressing gestational age. In a Cochrane review in 2017, they identified no studies that met their inclusion criteria [29–31].

At present, the optimal mode of preterm delivery for preeclampsia might be a trial of labor, resulting in 50% of success, which requires close monitoring of maternal and fetal conditions during the vaginal trial.

20.3 Complications of Cesarean Delivery for Preterm Birth

Cesarean delivery sometimes encounters difficulties to deliver the fragile preterm infants due to relatively thickened myometrium. In this situation, a vertical incision extended to the upper contractile part is helpful to deliver the fetus gently, resulting in a classical or reverse-T uterine incision. Previous studies showed an inverse relationship between gestational age at delivery and the likelihood of classical cesarean delivery. The incidence of classical cesarean delivery is reported as approximately 0.3–1% of all deliveries [32–34]. An Australian study noted that at 24 weeks, 20% of all cesarean deliveries were of the classical type, while at 30 weeks, the rate was 5%, and at term, only 1% [32]. Compared with low transverse incisions, classical cesarean incisions are associated with a higher rate of subsequent uterine rupture (2.0% versus 0.7%) and increased up to 9% during attempts at the trial of labor [33]. Cesarean section of woman who had a history of classic and inverted T cesarean incisions is usually planned at 36–38 weeks of gestation to avoid uterine rupture, while the incidence of prelabor uterine rupture was reported to be about 2% in a prospective multicenter study [35]. From 2008 to 2011, Reddy and colleagues assembled an observational obstetric cohort from 25 hospitals in the USA [36]. They determined the prevalence of serious maternal complications of deliveries between 23 and 33 weeks gestation, based on data selected randomly representing one-third of deliveries. They defined serious maternal complications as hemorrhage ($\geq$1500 mL, blood transfusion, or hysterectomy), infection, intensive care unit admission, or death. Of 2659 women, 8.6% of them experienced serious maternal complications associated with gestational age which were highest during 23–27 weeks of gestation. Associations between maternal complications and the uterine incision sites were also revealed; 3.5% by vaginal delivery, 23.0% by classic, 12.1% by low transverse incision, and 10.3% of low vertical cesarean delivery.

20.4 Conclusions

Most previous reports showed that maternal and neonatal outcomes do not differ based on the intended mode of delivery. However, the optimal delivery method for preterm infants has not yet been concluded. Induction of labor should be considered

when early preterm birth is indicated as long as the fetus is reassuring with vertex presentation. In cases of breech presentation or multifetal pregnancy, cesarean delivery might be considered. The morbidity and mortality rate among premature neonates are different in each country and even in facilities. Physicians need to discuss and explain with the patient about the benefits and risks of cesarean delivery and prepare for some potential risks such as hemorrhage, infection, and intensive care unit admission.

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Premature Rupture of Membranes

21

Koichiro Shimoya

Abstract

In pPROM, complications such as fetal immaturity and intrauterine infection may occur, and intensive care that is distinct from that of full-term PROM is required. pPROM occurs in 25% of all PROMs, and approximately 30% of premature births involve pPROM. There are two causes of premature membrane rupture. One is the abnormality of the fetal membrane due to ascending infection from the lower reproductive organs. Another cause of premature rupture of membranes is the elevation of intrauterine pressure. The following management such as avoiding frequent internal examination, antibiotic administration, administration of adrenal steroid hormones if delivery is predicted to be between 22 and 34 weeks of gestation, confirmation of amniotic fluid volume and fetal growth by ultrasound, and fetal heart rate monitoring is considered. There are options of delivering the newborn if gestational age is more than 34 weeks and options to wait or to induce delivery after 24 h of waiting if premature rupture of membranes occurs in full-term pregnancy to manage PROM.

Keywords

pPROM · Infection · Elevation of intrauterine pressure

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21.1 Outline

Rupture of the fetal membranes before the onset of labor is called premature rupture of membranes (PROMs). PROM can develop at any time during the gestational period; however, when it occurs at less than 37 weeks of gestation, it is called preterm PROM (pPROM). Management of pPROM is different from that of PROM. Premature rupture that occurs at 37 weeks or later usually results in natural labor and normal delivery, and clinical obstetric and gynecological problems rarely occur. In pPROM, complications such as fetal immaturity and intrauterine infection may occur, and intensive care that is distinct from that of full-term PROM is required.

21.2 Pathology

During pregnancy, the fetus is surrounded by the amniotic membrane and buffered from shock by the amniotic fluid. In addition to this, pressure on the umbilical cord should also be avoided to maintain a steady supply of oxygen and nutrients to the fetus. The amniotic membrane separates the fetal environment from the outside environment and protects the fetus from any ascending infection from intrauterine bacteria and microorganisms.

Premature rupture of membranes occurs in 3–18% of all pregnancies and in about 10% of full-term pregnancies. pPROM occurs in 25% of all PROMs [1], and approximately 30% of premature births involve pPROM [2]. The period from PROM to the onset of labor (latency period) is inversely correlated to gestational age.

For pregnancies 28–36 weeks of gestation, 50% go into labor within 24 h, and 80–90% within 1 week. For pregnancies less than 26 weeks of gestation, approximately 50% go into labor within 1 week [3].

The structure of the fetal membrane consists of 4–6 chorion membranes and an amniotic membrane made up of a single layer of cells. These maintain the integrity of the membrane structure, but when the cells and connective tissues that constitute the membrane undergo pathological degeneration, the membrane collapses. There are two causes of premature membrane rupture. One is the abnormality of the fetal membrane due to ascending infection from the lower reproductive organs. Chorioamnionitis develops, and the proteolytic enzymes produced by migrating white blood cells weaken the collagen of the fetal membrane, leading to PROM. Premature birth is usually caused by intrauterine infection. However, the prevalence of amniotic bacteria in premature birth is 16.1%, while it is reported to be at 27.9% in pPROM. Hence, it is understood that infection plays an important role in pPROM. The inflammatory mediators induced by infection cause uterine contraction, and it is thought that the softening of the cervix that shifts the chorion and amniotic membrane is the cause of membrane rupture. It is also thought that maternal or fetal stress leads to the production of corticotrophin-releasing hormone (CRH) via the stress-dependent hypothalamus–pituitary–adrenal axis, and may also be a trigger of pPROM. Another cause of premature rupture of membranes is the

elevation of intrauterine pressure, which could be caused by several factors, such as excessive amniotic fluid, multiple pregnancies, increased abdominal pressure due to cough, and uterine malformation. Intrauterine procedures such as amniocentesis, cordocentesis, and fetoscopic laser photocoagulation for twin-to-twin transfusion syndrome may also damage the fetal membrane and cause premature rupture of membranes.

21.3 Diagnosis

Diagnosis of PROM starts with taking a detailed medical history and physical examination before and after the rupture. In most cases, there are sudden fluid leaks out of the vagina and intermittent leaks thereafter. However, if most of the amniotic fluid flows out and does not remain in the vagina, it is very difficult to detect PROM. Furthermore, contamination with urine, cervical mucus, vaginal discharge, and blood makes it difficult to identify amniotic fluid. Sterile speculum examination confirms the presence of amniotic outflow from the opening of the uterus; this is a classical diagnostic method. Next, pooling of water-soluble liquid in the vagina is checked. In case of pooling, clinical measurement of the vaginal pH is widely performed; the pH of normal amniotic fluid is within the range of 7.1–7.3, which is different from that of the vagina with a pH of 4.5 or lower. This is also confirmed by the change in the nitrazine (Amnicater) reagent to a blue color, and this test is thought to be 90–98% accurate [4]. Attention should be paid to false positives due to blood contamination. In addition to the pH test, Fern test is also useful. As an adjunct diagnostic, ultrasound can be used to measure the volume of amniotic fluid volume. Biochemical diagnostic methods include fetal fibronectin (ROM check), α-fetoprotein (Amtec), and insulin-like growth factor-binding protein 1 (IGFBP-1, Amni test Meiji Milk). It is said to be useful when one is unsure if her water is breaking (PROM or pPROM). Dye injection test can be performed by injecting indigo carmine into the uterine cavity and observing for dye leakage if a definitive diagnosis of premature rupture of membranes or low amniotic fluid levels cannot be determined with these inspection methods.

21.4 Management (Treatment)

The problem with premature rupture of membranes during full-term pregnancy is that the risk of ascending intrauterine infection increases with the passage of time. Induced labor is required in cases when there are signs of infection already; however, 90% of pregnant women usually go into labor within 24 h. The decision of whether to induce labor immediately in preterm pregnancies or to wait is largely dependent on the wishes of the patient. However, it has been reported that, even if labor was induced, the rate of cesarean section does not increase, and the rate of intrauterine infection decreases [5, 6]. Furthermore, the risk of ascending intrauterine infection in the waiting group and the induced labor group was studied,

and the maternal infection rate was significantly less in the induced labor group than in the waiting group [7]. In contrast, the frequency of chorioamnionitis within 24 h of rupture in full-term pregnancy is less than 10%, but increases up to 40% after 24 h [8]. Therefore, in principle, it is not desirable to wait for a long time, and internal examination should be minimized to prevent infection. For full-term pregnancies with positive GBS results, penicillin antibiotics are administered as a rule.

Fetal immaturity is a serious problem following pPROM, and the patient should always be admitted to a hospital. Other complications occur frequently in pPROM due to low amniotic levels, including cord problems such as umbilical cord prolapse and umbilical cord compression and attention must be given to pulmonary hypoplasia and joint contractures. In terms of maternal infections, chorionic amniotic membrane infection is found in 13–60% of cases, followed by endometriosis and sepsis. In addition to this, premature ablation of the placenta occurs in 4–12% of pPROM, and postpartum hemorrhage is also recognized in 12% of cases [9]. The aim of the management of pPROM is to prolong the pregnancy period and to wait for fetal development and maturation while paying attention to signs of intrauterine infection, maternal infection, uterine contraction, and abnormal fetal heartbeat such as fluctuating transient bradycardia. In late preterm cases, the duration in which to continue with expectant treatment in the absence of infection is a controversial issue. However, if the pregnancy is more than 34 weeks of gestation, induced labor is considered as one of the options. If symptoms of infection appear after 26 weeks of pregnancy, it is common to stop expectant treatment and choose childbirth. Furthermore, it is necessary to carry out GBS culture in preparation for the delivery.

Expectant management treatment includes administration of uterine contraction inhibitors, antibiotics, and corticosteroids; however, the administration of uterine contraction inhibitors is also controversial. Evidence-based medicine reported that administration of a uterine contraction inhibitor has no effect on prolonging long-term pregnancy, and does not improve perinatal prognosis [10–12]. Therefore, if this is strictly applied, it is only appropriate to administer a uterine contraction inhibitor after observing the effects of administering an adrenal steroid as described below. However, in reality, it is believed that the continuous administration of uterine contraction inhibitors is done in many institutions, and in some cases, the effects are actually felt. The understanding of the scientific basis of its use is poor, and attention should be given to the possible side effects of its use. On the other hand, the use of magnesium sulfate as a preventive measure against brain damage (cerebral palsy) in preterm infants has been reported [13–16], and it appears that there is also room for considering its use in cases of pPROM.

To prevent intrauterine infection, antimicrobial drugs are administered for cases of premature rupture of membranes. In a large-scale NICHD study on the administration of antibiotics for pPROM, 2 g ampicillin and 250 mg erythromycin were intravenously infused every 6 h within 48 h of rupture, and 250 mg amoxicillin and 333 mg erythromycin were administered orally every 8 h for 5 days thereafter. It is possible to extend the gestation period of the antibiotic administered group; an

improvement in the prognosis of sepsis in the neonate and a decrease in cases of chorioamnionitis were seen [17]. Furthermore, ORACLE studies have reported that a combination of amoxicillin and clavulanic acid (e.g., Augmentin) increases neonatal necrotizing enterocolitis [18]. Therefore, it is recommended to administer antibiotics for 7 days only if treatment is based on EBM. Center for Disease Control and Prevention (CDC) recommends taking measures to prevent GBS infection for 48 h [19].

It is known that maternal administration of corticosteroids in pregnant women with premature labor improves the prognosis of the fetus, but in cases of pPROM, it is suggested that there is a possibility that the administration of steroids may exacerbate infection or that PROM pathology itself promotes fetal lung maturation. Although it remains controversial, current maternal administration of corticosteroid does not increase the risk of infection, and it has been shown to lower the morbidity and mortality rate of newborns [20]. If delivery is expected 24 to less than 34 weeks, two doses of 12 mg betamethasone are administered 24 h apart for pulmonary maturation and prevention of intracranial bleeding. Although it has not been proven to be effective for pregnancies with a gestation of less than 24 weeks, administration of betamethasone is still recommended [21].

21.5 Prognosis

The factor that determines the prognosis of newborn babies is gestational age, and extending the gestation period is important. In addition to this, the presence or absence of infection also greatly influences the prognosis of the child. The death rate of newborns that developed pulmonary hypoplasia due to rupture in early pregnancy is thought to be up to 90% [22].

21.6 Summary

Attention should be paid to the following points related to premature rupture of membranes:

- Confirmation of diagnosis
- Rules for hospitalization and treatment
- Avoiding frequent internal examination
- Antibiotic administration
- Administration of adrenal steroid hormones if delivery is predicted to be between 22 and 34 weeks of gestation
- Confirmation of amniotic fluid volume and fetal growth by ultrasound
- Fetal heart rate monitoring
- Option of delivering the newborn if gestational age is more than 34 weeks
- Options to wait or to induce delivery after 24 h of waiting if premature rupture of membranes occurs in full-term pregnancy

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Part V

Preterm Newborn

The Preterm Newborn: Morbidity and Mortality—Including a Population-Based Study in Miyazaki Prefecture

22

Yuki Kodama

Abstract

Neonatal and perinatal mortality has decreased dramatically in the past few decades. Neonatal mortality rate among all infants accounted for 1.26 per 1000 births in our region between 1998 and 2012. Of these, the mortality rate of preterm infants was 13.0 per 1000, while that of term infants was 0.51 per 1000 births. Compared with term infants, preterm infants have several more serious medical complications throughout the neonatal period, with the possibility of subsequent neurodevelopmental disorders. Most complications during the neonatal period arise from the underdevelopment of organs; these include conditions such as respiratory distress syndrome, chronic lung disease, necrotizing enterocolitis, and patent ductus arteriosus, retinopathy of prematurity, intraventricular hemorrhage, and periventricular leukomalacia. Other complications in the long-term include cerebral palsy and other neurodevelopmental disorders such as mental retardation, epilepsy, and sensory impairment (hearing, vision).

This chapter presents the major complications in preterm infants based on management in the neonatal intensive care unit at a tertiary medical center, and our regional population-based study conducted in Miyazaki Prefecture, Japan.

Keywords

Periventricular leukomalacia · Intraventricular hemorrhage · Perinatal mortality · Cerebral palsy · Brain damage

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22.1 Epidemiology

Infant mortality has decreased tremendously over the past 30 years owing to advances in perinatal and neonatal care. In our regional population-based study in Miyazaki Prefecture, Japan, between 1998 and 2012, neonatal mortality rate decreased significantly at 5-year intervals [1]. Neonatal mortality in all infants accounted for 1.26 per 1000 births. Of these, the mortality rate for preterm infants was 13.0 per 1000, while that of term infants was 0.51 per 1000 births. In most perinatal centers in developed countries, neonatal deaths are uncommon for infants of birth weight >1000 g without any congenital anomalies. Survival rate by gestational age during the period between 2005 and 2015 in Miyazaki University Hospital was as follows: 22 weeks, 44%; 23 weeks, 85%; 24 weeks, 83%; 25 weeks, 94%; 26 weeks, 98%; 27 weeks, 93%; and 28 weeks, 95%. Nevertheless, preterm infants develop several complications during the neonatal period as well as morbidities extending to later in life (Table 22.1). These complications are primarily the consequence of underdeveloped organs.

22.2 Complications of Prematurity

22.2.1 Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is characterized by stiff non-compliant lungs with inadequate surfactant. During vaginal delivery, some of the fetal lung fluid is expressed and absorbed as the chest is compressed. The remainder is absorbed through the pulmonary lymphatics. At this time, pulmonary surfactant, which is produced by type II pneumocytes, plays a role in stabilizing the alveoli as they are expanded on inspiration. Surfactant lowers surface tension and thus prevents lung collapse during expiration [2]. Inadequate surfactant results in unstable alveoli that collapse under low pressure at the end of expiration. A hyaline membrane composed of fibrin-rich protein and cellular debris forms in the distal bronchioles and alveoli, and is the characteristic feature of RDS.

Table 22.1 Complications of preterm infant

Respiratory distress syndrome (RDS)
Chronic lung disease (CLD)/ bronchopulmonary dysplasia (BPD)
Pneumothorax
Pneumonia/sepsis
Patent ductus arteriosus (PDA)
Necrotizing enterocolitis (NEC)
Focal intestinal perforation (FIP)
Retinopathy of prematurity (ROP)
Intraventricular hemorrhage (IVH)
Periventricular leukomalacia (PVL)
Cerebral palsy (CP)

The clinical symptoms of typical RDS include tachypnea, intercostal retraction, grunting, and nasal flaring. Right-to-left blood shunting in the lung leads to hypoxemia and metabolic as well as respiratory acidosis. Chest radiography typically shows reticulogranular infiltrate and air bronchogram, which suggests an air-filled tracheobronchial tree.

22.2.2 Bronchopulmonary Dysplasia/Chronic Lung Disease

Bronchopulmonary dysplasia (BPD) was first described by Northway et al. [3] in 1967, as a chronic pulmonary disease following RDS treatment. BPD, also referred to as chronic lung disease (CLD) of prematurity, is considered a heterogeneous disorder, and its cause is multifactorial. Prolonged mechanical ventilation and hyperoxia have been associated with CLD. Infection also induces an inflammatory response with an altered milieu of growth and inflammatory factors. These continuing insults contribute to the long-term changes in lung structure that characterize CLD. The US National Institutes of Health reviewed the definition by categorizing the severity of CLD as mild, moderate, or severe [4]. Advances in neonatal medicine have enabled survival of the extremely premature infant. This might be responsible for the noted increase in infants with CLD. In the Canadian Neonatal Network, about 40% of extremely low-birth-weight (ELBW) infants have been reported to develop CLD, and a critical number of survivors are discharged home on supplemental oxygen [5]. The prevalence of CLD in ELBW infants was reported as 46.2% in 1995, 54.0% in 2000, and 59.0% in 2005 [6].

22.2.3 Patent Ductus Arteriosus

Cardiovascular stability is critically important immediately after birth. Clinical signs include poor skin perfusion with pallor and mottling, tachycardia, bradycardia, and low blood pressure. At our center, treatment consists of administering continuous infusion of low-dose dopamine and/or volume expanders to preterm infants with RDS. Indomethacin is also administered for the prevention of symptomatic patent ductus arteriosus (PDA), if indicated. Excessive fluid intake and late-onset sepsis have been associated with persistence of PDA [7]. Exogenous surfactant administration may lead to PDA because it could affect the rapid drop in pulmonary vascular resistance by improved pulmonary function, leading to a left-to-right shunt. Furthermore, genetic factors could also modulate ductal patency. The risks associated with left-to-right hemodynamically significant ductal shunt include pulmonary overcirculation (pulmonary edema, respiratory failure, pulmonary hemorrhage, and CLD), pulmonary vascular resistance changes (pulmonary hypertension), and systemic hypoperfusion (intraventricular hemorrhage, necrotizing enterocolitis, renal failure, and metabolic acidosis). The clinical signs of symptomatic PDA are hyperactive precordium, bounding pulse, wide pulse pressure, and heart murmur on auscultation.

Management of PDA in preterm infants is still controversial in terms of both prophylactic and therapeutic management. It remains to be determined how best to qualify PDA as clinically significant, and then how and when to treat it.

Medical treatment with cyclooxygenase inhibitors such as indomethacin or ibuprofen are primarily used if there are no contraindications, followed by surgical procedures as alternative or adjunctive treatment.

22.2.4 Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a grave disorder that affects not only premature but also term infants. The etiology of NEC is multifactorial and includes predisposing factors such as gastrointestinal immaturity, poor intestinal motility, hypoxemia, ischemia, PDA, umbilical catheter placement, small-for-date, feeding practices, feeding of cow milk and hypertonic solutions, exchange blood transfusion, and systemic infections [7]. Clinical findings of NEC include abdominal distention, increased gastric residuals, ileus, and bloody stools. Typically, bowel wall gas derived from invading bacteria results in pneumatosis intestinalis, seen on radiography. The modified Bell's criteria have been used to classify the severity of the disease. Initial treatment for NEC is to initiate antibiotics immediately after septic workup. The benefits of surgical treatment by either laparotomy or peritoneal drainage remain controversial; however, in an observational study, death rates and neurodevelopmental outcomes at age 18–22 months were lower with laparotomy compared with drainage [7].

22.2.5 Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is another complication in preterm infants and is the largest single cause of childhood blindness globally. The incidence and severity of ROP is inversely proportional to birth weight and gestational age [7]. Severe ROP is defined as that requiring laser or bevacizumab (Avastin) therapy in at least one eye. Arterial oxygen tension remains a major risk factor for ROP, despite the use of continuous pulse oximetry and the presumed tighter control of arterial pO_2. Avoiding fluctuations from normoxemia to hyperoxemia and to hypoxemia has been reported to decrease the incidence of ROP [7]. At our institution, we set the range of SpO_2 at between 85% and 93% and try to avoid fluctuations in the extremely preterm infant.

Recently, the use of intraocular bevacizumab (Avastin) injection has increased as an alternative to laser photocoagulation therapy; details regarding this therapy, such as dosing and side effects in the short- and long-term, need to be clarified.

22.2.6 Intraventricular Hemorrhage

There are four major categories of intracranial hemorrhage in a newborn infant [8]. Subdural hemorrhage is the result of trauma; subarachnoid hemorrhage and

cerebellar hemorrhage result from trauma in term infants and hypoxia in preterm infants. Periventricular–intraventricular hemorrhage results from either trauma or asphyxia. Intraventricular hemorrhage (IVH) originates in the subependymal germinal matrix. Choroid plexus hemorrhage occurs in nearly 50% of infants with germinal matrix hemorrhage and IVH [8]. IVH is a major cause of morbidity and mortality, especially in extremely preterm infants. The severity of IVH was first classified by Papile et al. [9]. Currently, the more widely used grading system is that proposed by Volpe [8]. Periventricular hemorrhagic lesions have been described as an "extension" of IVH. The pathogenesis of periventricular hemorrhage infarction is considered to be that the IVH or its associated germinal matrix hemorrhage causes obstruction of the terminal veins and results in impaired blood flow in the medullary veins, leading to hemorrhagic venous infarction [8]. The etiology of periventricular hemorrhage is multifactorial and includes hypoxic-ischemic events, anatomical factors, and coagulopathy among others. Severe IVH has serious potential sequelae in infants who survive, including hemorrhagic periventricular infarction, posthemorrhagic hydrocephalus, seizures, periventricular leukomalacia (PVL), and neurodevelopmental impairment. The overall incidence of IVH has been reported to have declined in recent years.

22.2.7 Periventricular Leukomalacia

This pathologic description refers to cystic areas deep in the white matter in the brain that develop after hemorrhagic or ischemic infarction (Fig. 22.1). The resulting tissue ischemia leads to regional necrosis. Generally, these features require at least 2 weeks to form, but may develop as long as 4 months after the initial insult [2]. Thus, if present at birth, it is clear that the insult could have occurred during pregnancy. Periventricular leukomalacia is thus helpful in determining the timing of the insult.

22.2.8 Cerebral Palsy

Neurodevelopmental impairment such as cerebral palsy (CP), mental retardation, sensory impairments (hearing, vision), and significant developmental delays could also occur in preterm infants. CP refers to a group of conditions characterized by chronic movement or posture abnormalities that are cerebral in origin, develop early in life, and are nonprogressive [10]. These abnormalities are classified by the type of neurological dysfunction as spastic, dyskinetic, or ataxic as well as by the number and distribution of limbs involved as quadriplegia, diplegia, hemiplegia, or monoplegia. Epilepsy and mental retardation frequently accompany CP.

The prevalence of CP has not changed over the past 50 years despite a sixfold increase in Cesarean sections [11]. Also, the widespread use of electronic fetal heart rate monitoring has not led to a decrease in the incidence of CP [12, 13]. In preterm infants, the prevalence of brain damage increased in the 1970s and 1980s as a result of increased survival due to advances in perinatal and neonatal

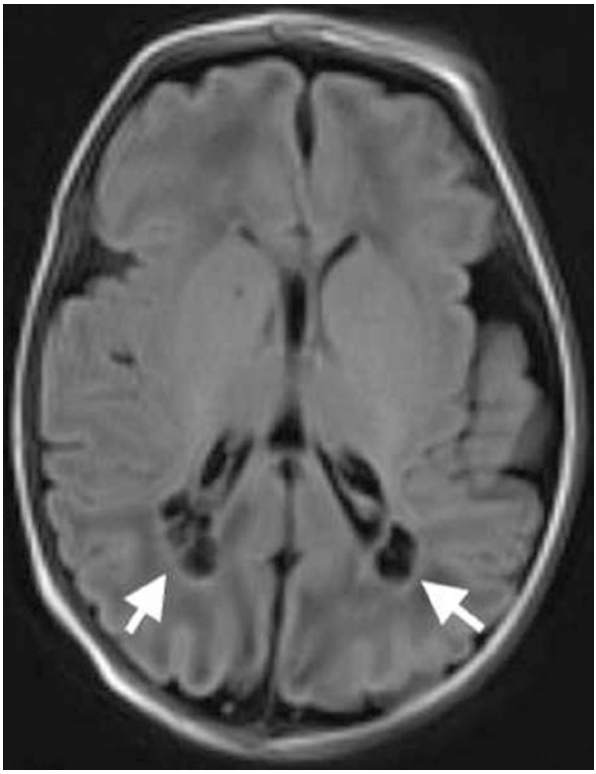

Fig. 22.1 Periventricular leukomalacia on MRI findings (arrows)

care [14–17]. Nevertheless, CP rates are reported to have decreased in recent years [7]. The incidence of neurosensory impairment decreased from 18% (1982–1989) to 9% (2000–2002), and also CP rate decreased from 8% to 5% observed 20 months of ELBW infants [18].

22.3 Population-Based Data in Miyazaki Prefecture

Miyazaki Prefecture, located in the southern part of Japan, has the lowest perinatal and neonatal mortality rates in Japan as of 2017. We have been conducting population-based research on perinatal outcomes of all pregnancies ≥22 weeks of gestation since 1998. During this 15-year study period (1998–2012), the number of registered CP cases was 312 of 156,766 live births (0.20%). These included extremely preterm (22–25 weeks) infants (n = 45), very preterm (25–27 weeks) infants (n = 34), moderately preterm (28–33 weeks) infants (n = 81), late preterm (34–36 weeks) infants (n = 40), and term (≥37 weeks) infants (n = 112) [19]. The number of live births and prevalence of CP in each group is shown in Fig. 22.2. In term infants, the prevalence of CP was 0.4 per 1000 live births, while in late preterm

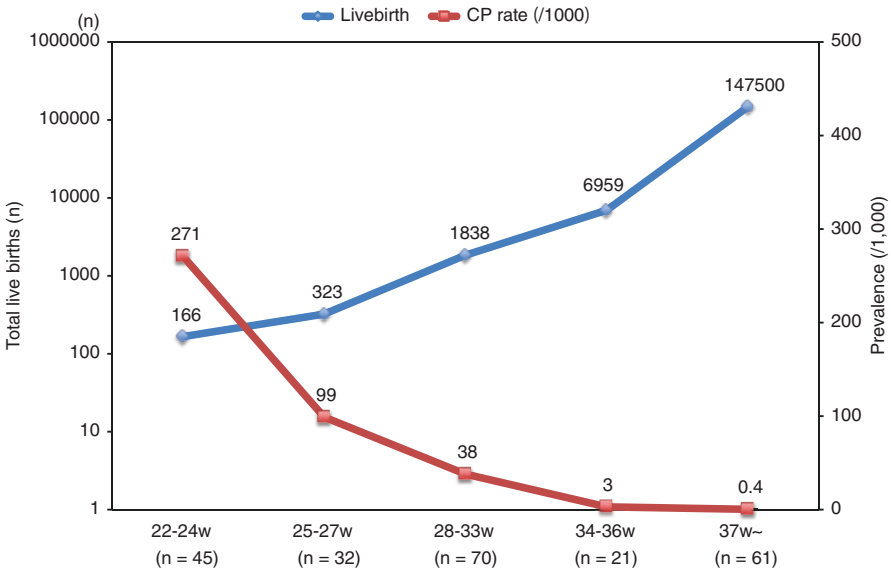

Fig. 22.2 Prevalence of cerebral palsy in each gestational age group, excluding congenital malformation (1998–2012). The prevalence of CP was 0.4 per 1000 live births in term infants, 3.0 per 1000 in late preterm infants, and 271 per 1000 in extremely preterm infants. (Redrawn from Yamashita [1])

infants, it rose to 3.0 per 1000 live births. It increased exponentially to 271 per 1000 in extremely preterm infants. The backgrounds of infants with CP were: PVL (26%), complications of prematurity (23%) such as IVH and NEC, and the presence of a congenital anomaly (18%) in preterm infants, and the presence of a congenital anomaly (45%), followed by hypoxia (33%) in term infants. Congenital malformations in preterm infants are less common compared with those in term infants, but are much more serious in preterm infants.

22.4 Future Directions

In our regional population-based study encompassing 15 years, we found that perinatal mortality had improved significantly with improving neonatal mortality rate. This observation is consistent with findings from previous reports [14, 17, 20–22].

Nonetheless, countermeasures based on gestational age are still required in order to prevent brain damage. And there is also the need to reduce the overall incidence of CP as well as perinatal death. Epidemiologically, the maternal use of magnesium sulfate has been reported to have a fetal neuroprotective effect. Thus, measures to improve the outcomes of prematurity, PVL, asphyxia in preterm infants are requisite. Clinical studies focused on these high-risk factors need to be investigated.

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Part VI

Placental Pathology

Placental Pathology

23

Yuichiro Sato

Abstract

Preterm labor is a multifactorial syndrome that can lead to long-term complications for the child. Intrauterine inflammation (placental infectious disease) is commonly noted in preterm labor cases. Acute placental inflammation is classified into maternal and fetal inflammatory responses. Placental examination is mandatory in case of abortion, preterm delivery, fetal malformation, infection, growth restriction, preeclampsia, late intrauterine death, intra-partum hypoxia, and complicated twin pregnancy. The histological system recently proposed by Redline is widely used to assess the severity of placental inflammation, including maternal and fetal inflammatory responses. There is a significant association between the fetal inflammatory response and neonatal conditions. Further, many cases of spontaneous preterm labor leading to preterm birth appear to be caused by placental insufficiency, similar to the case of preeclampsia and intrauterine growth restriction/fetal growth restriction. Placental insufficiency has also been implicated in other causes of preterm labor, including placental abruption, chronic intrauterine hemorrhage, chronic villitis, and chronic intervillositis.

This chapter focuses on the pathological diagnostic features of preterm labor, including the placental inflammation severity and placental insufficiency. The use of placental pathology to understand intrauterine conditions can improve early gestation diagnostic testing and revolutionize preventative care for mothers and newborns.

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Placenta · Pathology · Chorioamnionitis · Fetal inflammation · Placental insufficiency

23.1 Preterm Labor and Placental Pathology

Preterm birth is a multifactorial syndrome that is associated with a variety of risk factors and long-term health consequences for the child. From a pathophysiological perspective, preterm birth is a highly complex syndrome that is not completely understood. Placental examination is mandatory in cases of abortion, preterm delivery, fetal malformation, infection, growth restriction, preeclampsia, late intrauterine death, intra-partum hypoxia, and complicated twin pregnancy. To perform a placental examination, a pathologist must receive a written request from the clinician, along with the pregnancy history, gestation week, weight of the baby, maternal health during pregnancy, and indications for referral.

Placental pathology provides important diagnostic information to ascertain the cause of preterm birth. Salafia et al. [1] studied the histological features of placentas from 539 preterm deliveries and 214 term deliveries. They found a significantly high incidence of umbilical or chorionic vasculitis (fetal inflammation), decidual vasculopathy, and chronic villitis/villitis of unknown etiology (VUE) among the preterm delivery cases. Placental lesions, umbilical-chorionic vasculitis, decidual vascular abnormalities, and chronic vasculitis/VUE were observed in 96% of births between 22 and 28 weeks, 54% of births between 29 and 32 weeks, and 46% of births between 33 and 36 weeks. Chisholm et al. [2] examined 102 placentas and found an association between intrauterine placental infectious changes, particularly umbilical vasculitis and chorionic vasculitis, and the severity of preterm (gestational age <34 weeks; birth weight <200 g) infant illness. Placental insufficiency is a known cause of several obstetric syndromes, including preeclampsia and fetal growth restriction (FGR). In addition, other conditions, such as placental abruption, chronic intrauterine bleeding, and chronic inflammatory disease, may cause preterm birth.

We reviewed the placental pathology findings in preterm labor cases (Table 23.1), and discuss the potential of using placental examination to improve early gestation diagnostic testing and preventative care for both the mother and child.

23.2 Intrauterine Infections

Prenatal infections are important aspects of placental pathology [3, 4] because they cause placental changes. Although these infections are common and varied, some are difficult to detect during placental examinations. Intrauterine infection can occur via two routes. Most commonly, the infection ascends into the amniotic sac from the vagina or cervix or via the decidua. In some cases, the infection is carried to the placenta by the maternal blood flow (hematologic infection). Acute chorioamnionitis

Table 23.1 The association between clinical diagnosis and histological findings of the placenta in preterm labor

Clinical diagnosis	Histological placental findings
Intrauterine inflammation	Chorioamnionitis
	Funisitis
Hypertensive disorders of pregnancy	Maternal (decidual) vasculopathy
	Infarction
Intrauterine growth restriction	Infarction
	Maternal (decidual) vasculopathy
	Fetal vessel thrombosis
	Villitis of unknown etiology
	Hemorrhagic endovasculitis/endovasculosis
	Chronic histiocytic intervillositis
Abruption	Retroplacental hematoma
Chronic abruption-oligohydramnios sequence	Diffuse hemosiderin deposition

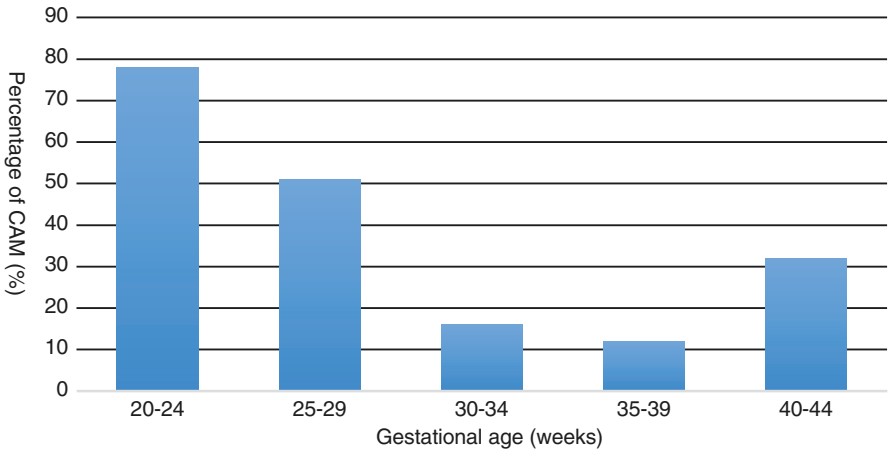

Fig. 23.1 The frequency of chorioamnionitis according to gestation age at the time of delivery

(CAM), membranitis, and funisitis indicate an ascending infection, whereas intervillositis or acute villitis indicates a maternal blood infection. Acute CAM is the most common diagnosis reported in placental reports and is generally considered to indicate the presence of intrauterine infection. The development of inflammation in the pregnant uterus involves several steps. First, the response to microorganisms is restricted to antigen non-specific cells, such as neutrophils and macrophages. Second, the inflammation tends to be confined to the peripheral area of the placenta, such as the membranes and terminal villi. Third, the fetal inflammatory response elicited by microbial antigens and other bacterial products damages fetal placental vessels and organs. CAM is associated with early delivery. Figure 23.1 shows the gestation age at the time of delivery in 522 cases of singleton pregnancies, wherein deliveries occurred after 20 weeks of gestation. The most deliveries occurred at a gestational age of 20–24 weeks (52/67 cases; 78%).

23.2.1 Chorioamnionitis

Typically, the CAM placenta is premature. Macroscopically, the color of the placenta and membranes appears to be normal in most CAM cases. If severe inflammation is present, the membrane may appear friable, edematous, opaque, and white-to-gray in color due to neutrophil exudation (Fig. 23.2). Long-term excess accumulation of leukocytic exudate causes the surface to become yellow. In addition, the membrane is typically more friable, and the decidua capsularis is frequently detached and hemorrhagic. These prematurely delivered placentas are often accompanied by acute marginal hemorrhage that originates from the deciduitis and undermines the edge of the placenta. In cases when CAM is detected in twin placentas, it is almost always the case that the cavity of twin A (first baby) is inflamed or contains the more severely inflamed portion. We have considered this to indicate that amniotic sac infections usually ascend through the cervical canal. Neutrophils are not normally present in the placental parenchyma or chorioamniotic membrane. The characteristic histological feature of CAM is the diffuse infiltration of neutrophils into the chorioamniotic plate or membrane. These leukocytes originate from two sources: the intervillous space (maternal leukocytes) and fetal surface blood vessels. Maternal neutrophils normally circulate in the intervillous space. In the presence of a chemotactic gradient, the neutrophils migrate toward the amniotic cavity, and the neutrophils in the subchorionic intervillous space mobilize in the chorionic plate of the placenta.

McNamara et al. [5] demonstrated that the neutrophils detected in CAM, with the exception of chorionic vasculitis, are of maternal origin by using fluorescence in situ hybridization (FISH) with probes for X and Y chromosomes. In contrast, Lee et al. [6] showed that the neutrophils in the umbilical cord and chorionic vessels of the placenta are of fetal origin. In addition, Sampson et al. [7] identified the neutrophils in the amniotic fluid to be of fetal origin.

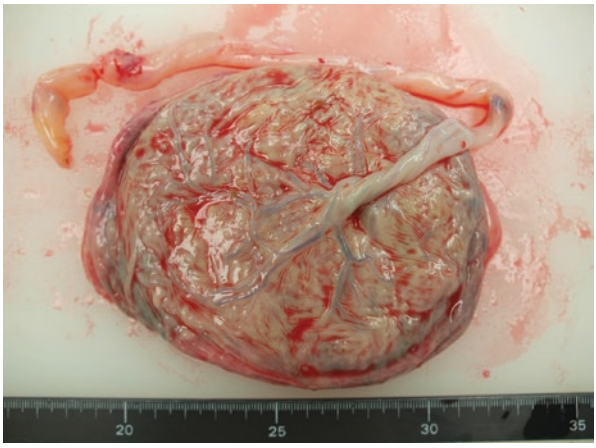

Fig. 23.2 Macroscopic appearance of chorioamnionitis. The amnion is white-to-gray in color

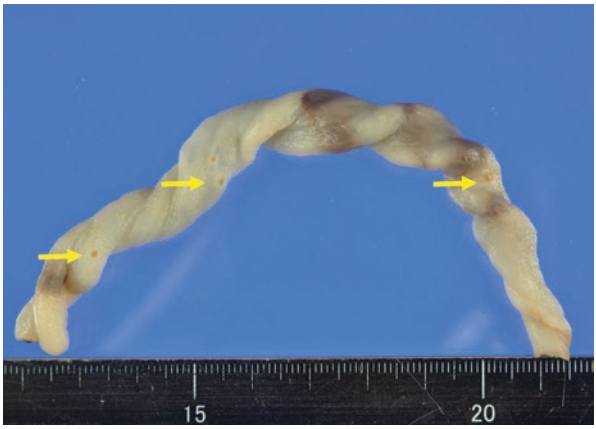

Fig. 23.3 Macroscopic appearance of *Candida* infection. Small white to yellow nodules can be seen (yellow arrows)

23.2.2 Funisitis

In early gestations, especially those prior to the 20th week of gestation, the neutrophils are mainly of maternal origin. By the midtrimester, the fetus is capable of producing leukocytes. Inflammation of the umbilical vessels begins in the vein (phlebitis), followed by involvement of the arteries (arteritis or funisitis). Neutrophil infiltration into the Wharton's jelly is common in acute funisitis. Tiny yellow-white nodules or plaques are observed on the umbilical cords infected with *Candida albicans* (Fig. 23.3). Microscopically, small accumulations of neutrophils with *Candida* hyphae are seen on the surface of the cord. Old exudate in the cord may accumulate in concentric perivascular rings. In cases of prolonged infection, mural thrombosis is frequently noted in the chorionic vessels. Thrombosis is noted in the umbilical cord in umbilical phlebitis, but is not commonly observed in umbilical arteritis.

23.2.3 Severity of Intrauterine Inflammation

Several grading and staging systems have been proposed to assess the severity of acute CAM. Histologically, intrauterine inflammation is generally divided into two categories: chorioamniotic membrane inflammation (maternal inflammation) and umbilical cord inflammation (fetal inflammation). Most systems that are designed to assess the severity of histological chorioamnionitis (CAM) have been based on the Blanc stage system [8]; however, this system has not been used to evaluate fetal inflammation. The classical CAM stage described by Blanc was found to be associated with chronic lung disease and intraventricular hemorrhage, but not with the occurrence of neonatal diseases after adjusting for gestational age [9].

Redline et al. [10] recently proposed a new histological system for grading both maternal and fetal inflammation according to the severity of the lesions (Table 23.2). They classified maternal and fetal inflammatory responses into stages and grades.

Table 23.2 Staging and grading system of acute chorioamnionitis and funisitis

	Maternal inflammatory response	Fetal inflammatory response
Stage 1	Chorionitis or subchorionitis	Umbilical phlebitis
Stage 2	Chorioamnionitis	Umbilical arteritis
Stage 3	Necrotizing chorioamnionitis	Necrotizing funisitis
Grade 1	Infiltration of individual or small clusters of neutrophils	Scattered neutrophil infiltration
Grade 2	Confluent neutrophil infiltration of at least 10–20 cells	Near-confluent neutrophil infiltration and/or degeneration of vascular smooth muscle cells

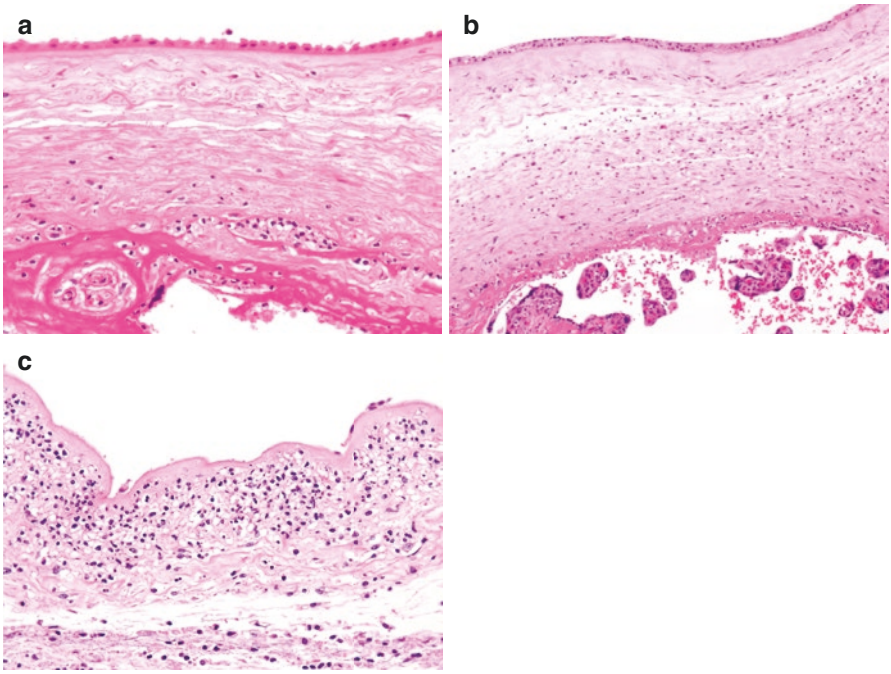

Fig. 23.4 Maternal inflammatory response stages. (**a**) Stage 1 (chorionitis or subchorionitis), (**b**) stage 2 (chorioamnionitis), (**c**) stage 3 (necrotizing chorioamnionitis)

Briefly, maternal stage 1 is characterized by the presence of neutrophils in the chorion (acute chorionitis) or subchorionic space (acute subchorionitis; Fig. 23.4a). Stage 2 refers to neutrophil infiltration in the amnion (acute CAM; Fig. 23.4b), and stage 3 is characterized by neutrophil infiltration and necrosis in the amnion (necrotizing CAM; Fig. 23.4c). Maternal grade 1 (mild to moderate) indicates the presence of individual or small clusters of neutrophil infiltration (Fig. 23.5a), and grade 2 (severe) involves confluent neutrophil infiltration comprised of at least 10–20 cells (Fig. 23.5b). Fetal stage 1 involves neutrophil infiltration in the chorionic vessel (chorionic vasculitis) or umbilical vein (umbilical phlebitis; Fig. 23.6a). Stage 2 involves neutrophil infiltration in the umbilical artery (umbilical arteritis; Fig. 23.6b)

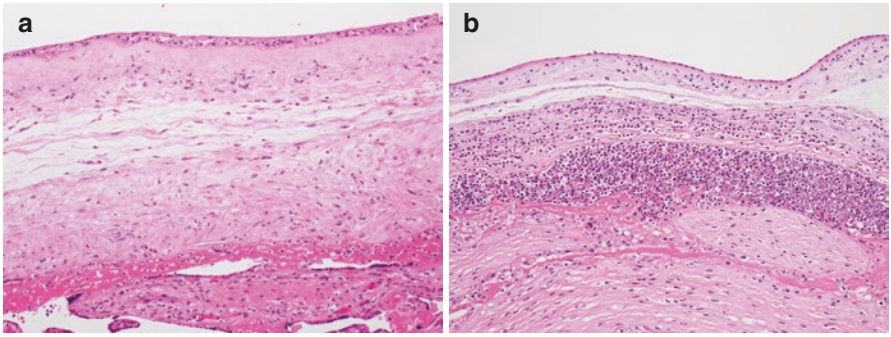

Fig. 23.5 Maternal inflammatory response grade. (**a**) Grade 1 (mild to moderate), (**b**) grade 2 (severe)

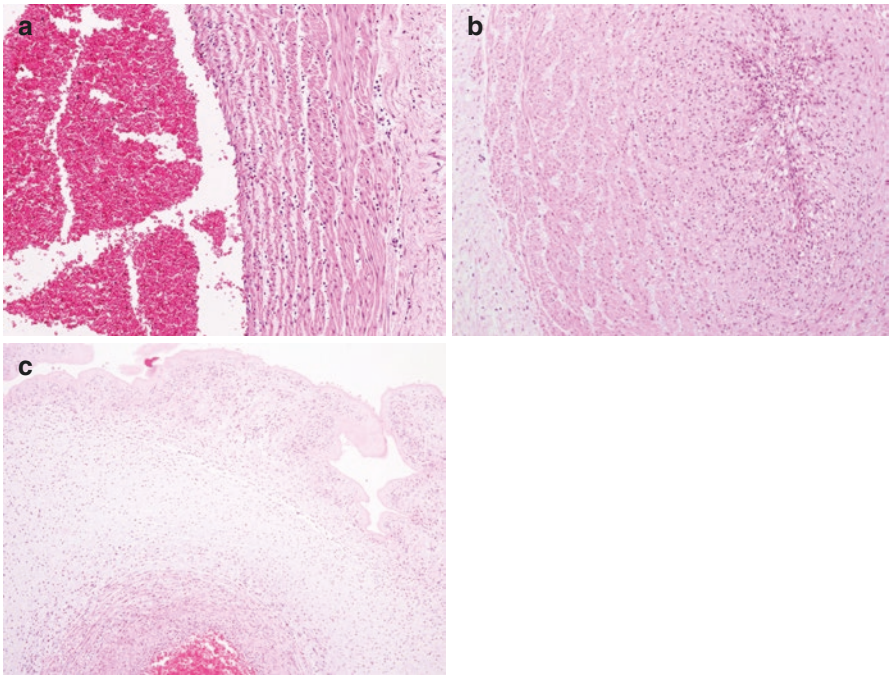

Fig. 23.6 Fetal inflammatory response stage. (**a**) Stage 1 (umbilical phlebitis), (**b**) stage 2 (umbilical arteritis), (**c**) stage 3 (necrotizing funisitis)

with or without phlebitis, and stage 3 is characterized by neutrophil infiltration with necrosis in the amnion (necrotizing funisitis; Fig. 23.6c). Fetal grade 1 (mild to moderate) is characterized by scattered neutrophil infiltration (Fig. 23.7a), and grade 2 (severe) is characterized by near-confluent neutrophil infiltration and/or degeneration of vascular smooth muscle cells (Fig. 23.7b). Zanardo et al. [11] reported that maternal stage 3 (necrotizing CAM) is associated with intraventricular

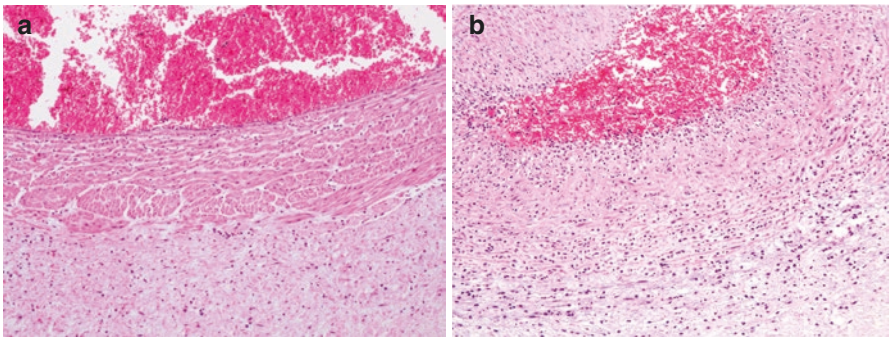

Fig. 23.7 Fetal inflammatory response grade. (**a**) Grade 1 (mild to moderate), (**b**) grade 2 (severe)

hemorrhage, and Lee et al. [12] showed that fetal inflammatory stage is associated with respiratory distress syndrome and bronchopulmonary dysplasia. We also used this system to assess placental findings in a study of 272 singleton neonates born at less than 34 weeks of gestation [13]. The incidence of sepsis, intraventricular hemorrhage, chronic lung disease, and necrotizing enterocolitis increased in a stepwise fashion with the severity of placental inflammation. After adjusting for gestational age, high grades of fetal inflammation were found to be significantly associated with chronic lung disease and necrotizing enterocolitis. Premature delivery is a major cause of perinatal mortality. Our study showed that higher stages and grades of maternal inflammatory responses were related to a shorter gestational age in CAM cases; in particular, the fetal inflammatory response was found to affect neonatal mortality.

23.2.4 Hematogenous Infections

Placental infection is rarely caused by infectious agents entering the organ via the maternal circulatory system. Generally, hematogenous infections involve the placental parenchyma rather than the membranes. Histologically, hematogenous infection is characterized by the presence of inflammatory lesions within the villous substrate, known as a villositis or villitis (Fig. 23.8). Villitis may be focal or diffuse. In acute villitis, the villi are infiltrated by neutrophils; however, in chronic villitis, lymphocytes, macrophages, or plasma cells are usually present.

23.3 Placental Insufficiency

Hypertensive disorders of pregnancy, typically defined as the de novo onset of hypertension and proteinuria after the 20th week of gestation, complicates approximately 2–8% of pregnancies [14]. The placenta in women with preeclampsia is smaller than that in women who have uncomplicated pregnancies. The overall

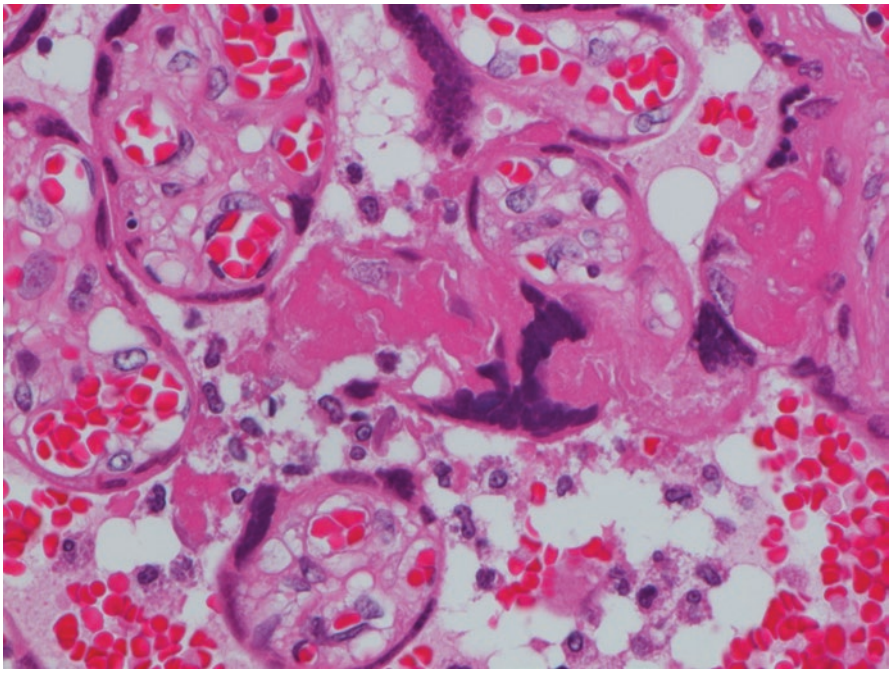

Fig. 23.8 Microscopic findings of hematogenous infection. Many neutrophils and macrophages are present in the intervillous space

incidence of placental infarction is much higher in preeclampsia cases than in uncomplicated pregnancies. The principal placental pathology changes in preeclampsia include maternal (decidual) vasculopathy, infarction in the central portion of the placenta, abruption, and Tenney-Parker change.

Intrauterine growth restriction (IUGR) or FGR manifests as low birth weight for a specific gestation period. IUGR is difficult to detect, and diagnosis usually involves a detailed assessment of maternal risk factors, including reproductive history, chronic conditions, pregnancy risk factors, and consecutive ultrasound findings. The placenta of babies with IUGR is small. Although IUGR is caused by several factors, reduced uteroplacental blood flow is a major cause. Further, primary intrinsic placental growth defects do not play a role in reduced placental growth. Placental insufficiency is a common cause of IUGR; however, fetal factors, including chromosomal abnormalities, congenital infections, and maternal risk factors, also contribute to IUGR.

Various pathological correlates, such as placental infarction, fetal vasculopathy/thrombosis, maternal vasculopathy, and chronic villitis, have been identified in IUGR cases [15]. In a previous study [16], we compared Japanese IUGR placentas (257 cases) with control placentas (normal growth pregnancies; 258 cases) and found the IUGR placentas to be smaller (296 g vs. 373 g, $P < 0.001$). With regard to histological findings, the prevalence of infarction (33% vs. 14%,

$P < 0.05$), fetal vessel thrombosis (22% vs. 6%, $P < 0.001$), and chronic villitis/VUE (11% vs. 3%, $P < 0.001$) was higher in the IUGR cases than in the controls. Other studies also demonstrated a high incidence of infarction, maternal infarction, and VUE in IUGR/FGR cases; however, acute CAM was not found to be associated with IUGR/FGR.

23.3.1 Maternal Vasculopathy

Maternal or decidual vasculopathy comprises a group of related pathological changes in the spinal arteries of the maternal decidua, including acute atherosis, hyalinization, and mural or occlusive thrombosis. Acute atherosis and preeclampsia placentas maybe of a normal size, but they are often smaller than average. Infarcts are common. Microscopically, smooth muscle cells of the vascular media persist. Acute atherosis is characterized by mural fibrinoid necrosis and the accumulation of large, foamy, lipid-filled macrophages and neutrophils (Fig. 23.9). Occlusive and mural thrombi are common. Ultrastructural studies of the placental bed vessels reveal endothelial injury. Distinct alterations are commonly seen in the villi of placentas associated with maternal preeclampsia and other states of maternal vascular perfusion.

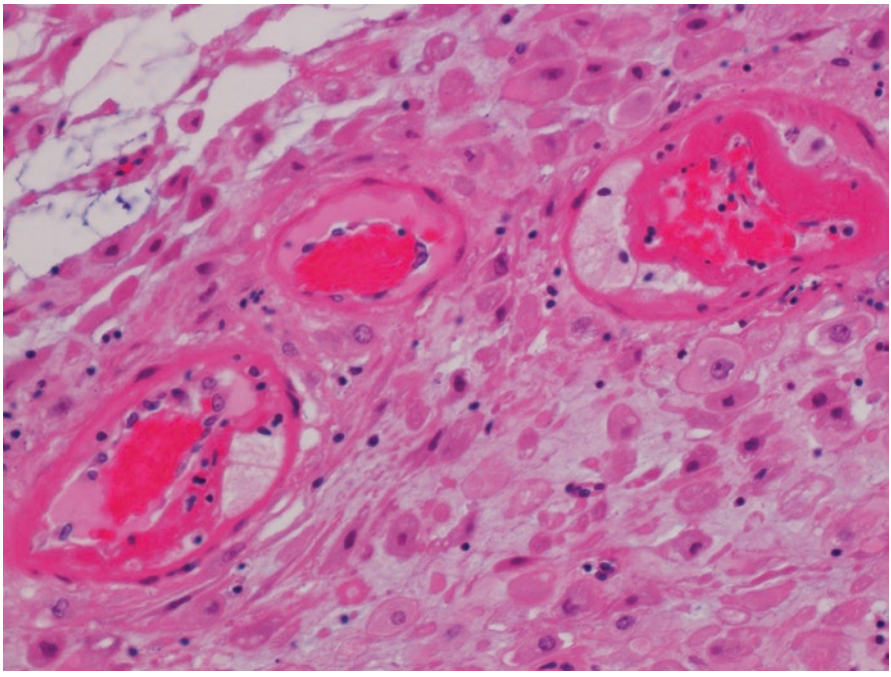

Fig. 23.9 Microscopic appearance of acute atherosis. The arteries show fibrinoid degeneration and accumulation of foamy macrophages

23.3.2 Infarction

Placental infarctions are localized regions of ischemic necrosis of the villi. Macroscopically, infarctions are circumscribed and firmer than the adjacent placenta. Recent infarctions appear dark red with only slight induration, and have a homogeneous or solid-appearing cut surface. These infarctions can be distinguished from living tissue by their firmness and lack of a spongy texture. Older infarctions are more indurated and demarcated, and progressively turn brown, tan, and finally white in color. Microscopically, necrosis of the villi is noted in the infarcted area (Fig. 23.10). In acute infarctions, villi are clustered together and are attached to one another by fibrin strands. The extreme ischemia also produces prominent trophoblastic knots. In old or chronic infarctions, the nuclear membranes of the trophoblasts and stromal and endothelial cells disappear. Phagocytosis of necrotic cells, organization, and fibrosis are observed.

23.3.3 Tenney-Parker Change

Tenney-Parker change (aggregation of syncytiotrophoblastic nuclei) is often noted in cases of placental insufficiency, such as preeclampsia or FGR. The placental stem villi are often slender with reduced branching; the terminal villi are very small and

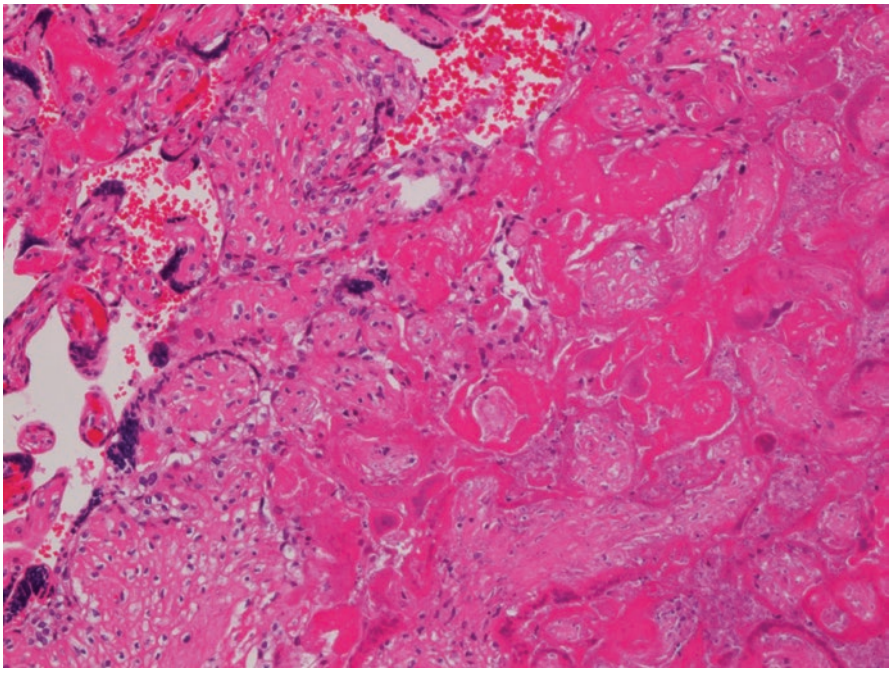

Fig. 23.10 Microscopic appearance of infarction. Coagulative necrosis of the villi (nuclei loss) is noted on the right side, and Tenney-Parker change is observed on the left side

produce a stunted or atrophic-appearing pathological pattern. This combination of findings has been termed as accelerated maturation.

23.3.4 Fetal Vessel Thrombosis

Fetal vessel thrombosis is associated with placental insufficiency, such as in the case of FGR, or stillbirth. Mural thrombi occur frequently in the superficial placental vessels and stem vessels, but occlusive thrombi are rare. Macroscopically, thrombotic occlusion areas on the chorionic or stem vessels with avascular villi (fetal thrombotic vasculopathy [FTV]) appear rough or sharply pale. Mural fetal vessel thrombosis is common, but FTV is rare.

Microscopically, fetal vessel thrombi are usually mural thrombi with some degree of organization (Fig. 23.11). Mural thrombi attach to the vascular wall without endothelial cells, and fibrous intimal thickening (endothelial cushion) is occasionally noted. Such thrombi often calcify over a prolonged duration. Old thrombi may get completely obliterated, and they may be difficult to detect among completely organized thrombi with fibrin strands. If the large thrombi have been occlusive for a prolonged duration, the entire villous tree may become avascular and atrophic and undergo fibrosis (FTV). However, avascular villi are occasionally

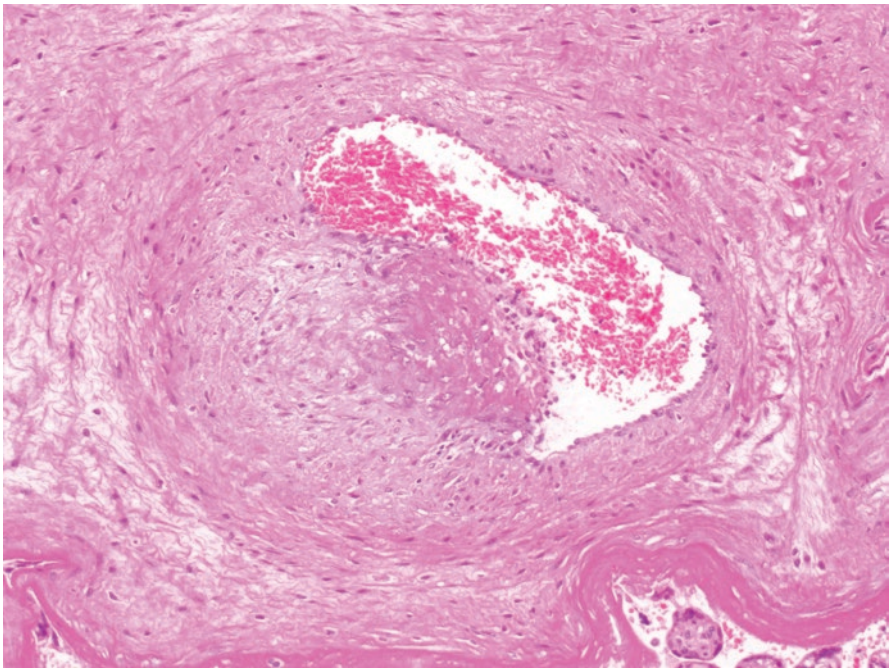

Fig. 23.11 Microscopic appearance of fetal vessel thrombosis. Mural thrombosis with organization (endothelial cushion) is present in the fetal vessel

found in many diseases and otherwise normal placentas. Redline and O'Riordan [17] proposed that the minimal criterion for FTV was the presence of ten or more small foci of three to five avascular villi.

Fetal vessel thrombi are variably located across the fetal surface within the placenta, and are only occasionally present in the umbilical cord. The thrombi are usually found in the umbilical vein associated with the intrauterine infection but have been reported to occur in the umbilical arteries as well. We previously reported on 11 cases of umbilical artery thrombosis [18]. In that study, the majority of umbilical artery thrombi were found in one artery, and atrophy of the umbilical arteries and mural ischemic degeneration of the vascular wall were noted. These thrombi were found to be associated with severe FGR or fetal mortality.

23.3.5 Hemorrhagic Endovasculitis/Endovasculosis

According to Sander et al. [19, 20], this fetal vessel abnormality is characterized by various degrees and combinations of stem vessel wall disruption with erythrocyte fragmentation, obliteration of villous capillaries, and thrombi in the stem vessels (Fig. 23.12). This fetal vessel disease is reportedly associated with a majority of stillbirth cases (>80%). However, placentas from liveborn infants also have this focal lesion, and it is usually associated with VUE, chorionic thrombi, or infarction.

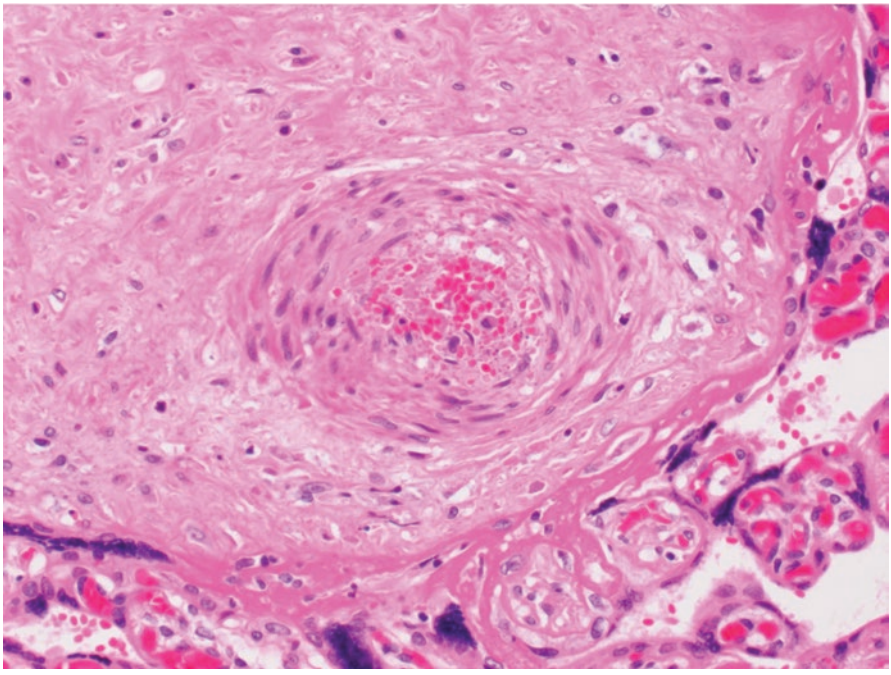

Fig. 23.12 Microscopic appearance of hemorrhagic endovasculitis/endovasculosis. The stem vessel exhibits obliteration with erythrocyte fragmentation

23.4 Intrauterine Hemorrhage

Intrauterine hemorrhage (placental abruption/retroplacental hematoma and diffuse hemosiderin deposition) is associated with preterm labor. Other intrauterine hemorrhage lesions are known as massive subchorionic thrombosis or intervillous thrombosis. We will focus on placental abruption/retroplacental hematoma and diffuse hemosiderin deposition.

23.4.1 Placental Abruption/Retroplacental Hematoma

Retroplacental hematoma occurs between the basal plate of the placenta and the uterine wall. Placental abruption refers to the clinically symptomatic state of premature placental separation with pain, bleeding, and accelerated uterine enlargement in the mother. Symptomatic placental separation may be extensive and occur suddenly. In classical abruption, the placenta has fresh clot attached at the maternal surface (Fig. 23.13). Older retroplacental hematomas are firm and brownish in color; further, the overlaying placenta is usually infarcted if the hematoma is large. The villous tissue is usually compressed by the hematoma and infarction, or ischemic changes of the villous tissue are noted. Maternal vasculopathy may also be observed.

23.4.2 Chronic Abruption-Oligohydramnios Sequence/Diffuse Hemosiderin Deposition

Abruption placenta is acute placental hemorrhage, leading to acute breakdown of placenta functions, such as fetal blood oxygenation. In contrast, chronic placental hemorrhage is not lethal to the fetus, and the pregnancy period can be prolonged with the administration of appropriate medication. Chronic placental hemorrhage is associated with oligohydramnios, as is termed as chronic abruption-oligohydramnios sequence (CAOS), which typically results in preterm delivery at approximately 28 weeks of gestation.

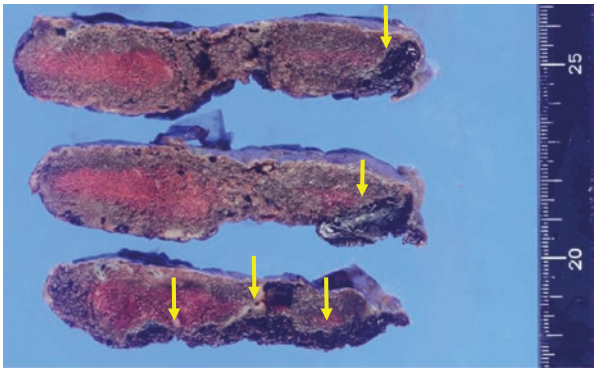

Fig. 23.13 Macroscopic appearance of a retromarginal hematoma. The hematoma compresses the parenchyma of the placental tissue

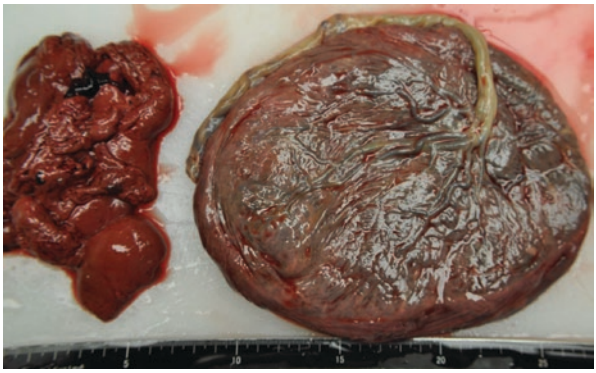

Fig. 23.14 Macroscopic appearance of diffuse hemosiderin deposition. The amnion is gray to greenish in color

Redline and Wilson-Costello [21] described the diffuse iron-stain positive pigment deposition in the chorioamniotic layers of the chorionic plate and/or membranes as diffuse chorioamniotic hemosiderosis (DCH). They reported a correlation between DCH and circumvallation and old peripheral blood clots, and proposed that DCH is an objective indicator of chronic peripheral separation and clinical CAOS. Ohyama et al. [22] analyzed DCH placentas and reported macroscopic findings of old peripheral blood clots (DHC: 46% vs. control: 8%), subchorionic hematoma (20% vs. 1%), and circumvallation (13% vs. 1%). With regard to microscopic findings, amniotic necrosis was significantly more frequent in the DHC group (63% vs. 24%). The incidence of recurrent episodes of vaginal bleeding (70% vs. 11%) and oligohydramnios (59% vs. 8%) was significantly higher in the DHC group.

The DCH placenta is brown to green in color in the amniotic membrane and exhibits circumvallation and old peripheral blood clots (Fig. 23.14). Microscopically, diffuse marked hemosiderin deposition is noted in the chorioamniotic plate or membrane, which is caused by the phagocytosis of hemoglobin or the products of hemoglobin breakdown by macrophages. Marked degeneration or necrosis of the amnion is also noted.

23.5 Chronic Inflammation of Unknown Etiology

Chronic inflammation lesions of the placenta are characterized by the infiltration of chronic inflammatory cells (lymphocytes, plasma cells, and/or macrophages), and may result from infections or be of unknown etiology (probably due to immunological reasons such as maternal anti-fetal rejection). Chronic inflammation lesions of the placenta that have an unknown etiology are known as VUE and chronic histiocytic intervillositis (CHI).

23.5.1 Villitis of Unknown Etiology

VUE is a T-cell-mediated disorder targeting the distal villous tree. It is characterized by chronic cellular inflammation of the villous stroma (villitis), intervillous space (intervillositis and perivillous fibrin deposition), and stem villous vessels

(obliterative fetal vasculopathy) [23]. VUE is a common lesion and occurs in approximately 3–5% of all term placentas. Immunohistochemical and in situ hybridization studies have shown that VUE represents a maternal immune response occurring within the fetal tissue, and the infiltrating lymphocytes are primary maternal T lymphocytes [24]. Clinically, VUE is associated with IUGR/FGR [23]. Antenatal fetal abnormalities are more common in pregnancies with diffuse VUE. The incidence of diffuse VUE is significantly higher in the placentas of term infants with cerebral palsy and other forms of neurogenic impairments.

Macroscopically, almost all placentas with VUE are normal, but some placentas are small for the gestational age and may exhibit a pale discoloration. In VUE, the microscopic findings include an infiltration of maternal T cells and an increasing number of fetal macrophages in the intermediate and terminal villi (Fig. 23.15); this is noted more commonly in the basal villous tissue (approximately 50% of cases). Basal villitis involves the anchoring of villi to the basal plate, and this type is frequently associated with chronic deciduitis. The proximal type occurs in 30% of cases and involves the proximal stem villi; this type is associated with obliterative vasculopathy and fetal vascular thrombo-occlusive disease, which results in hyalinized avascular villi. The histological grading of VUE is based on the number of affected chorionic villi [23]. Approximately two-thirds of VUE cases involve small clusters of five to ten villi in either a single (focal) or multiple (multifocal) slides.

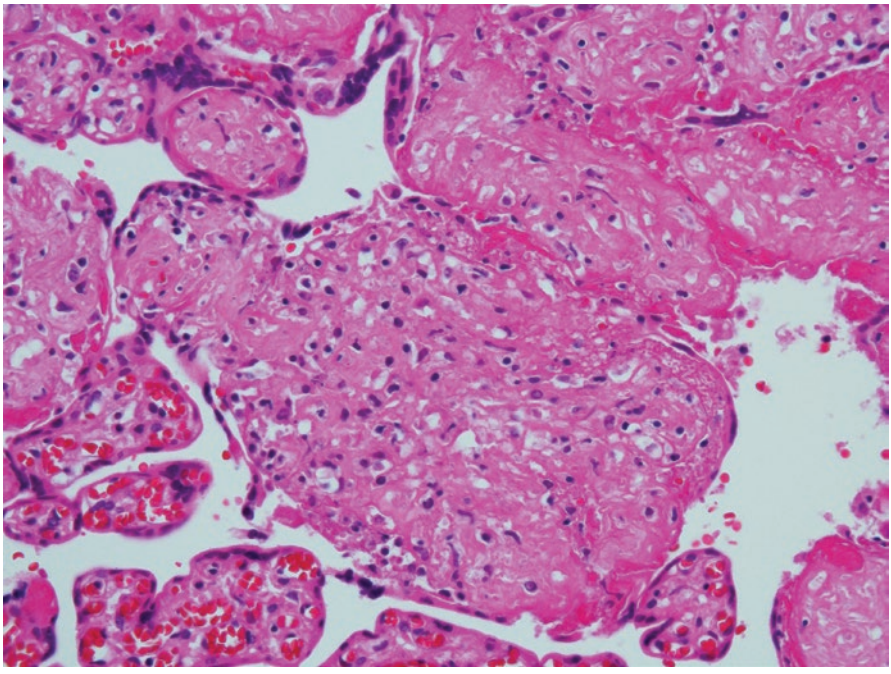

Fig. 23.15 Microscopic appearance of villitis of unknown etiology. Many chronic inflammatory cells infiltrate the terminal villi. The villi exhibit fibrosis and capillary loss

These low-grade patterns are usually clinically silent. The remaining cases involve larger (more than ten villi) foci (patchy) and diffuse involvement of all sections (diffuse). A strong relationship has been demonstrated between these high-grade patterns and FGR and other clinical complications.

23.5.2 Chronic Histiocytic Intervillositis

CHI is a rare placental lesion characterized by marked infiltration of maternal chronic inflammatory cells into the intervillous space, which can be accompanied by varying degrees of intervillous fibrin deposition. This entity, first described by Labarrete and Mullen in 1987 [25], consists of recurrent lesions and is associated with a poor pregnancy outcome; however, despite anecdotal reports of successful immunomodulatory treatment, no effective treatment is available [26]. The reported incidence of CHI is 4.4% in first trimester miscarriages with a normal karyotype and is quite rare in the second or third trimester. The true incidence of CHI, however, is still unknown. The mechanism underlying these associations is still unclear. Further, a hypothesis of immune conflict was proposed, but is yet to be proven [27] (Fig. 23.16).

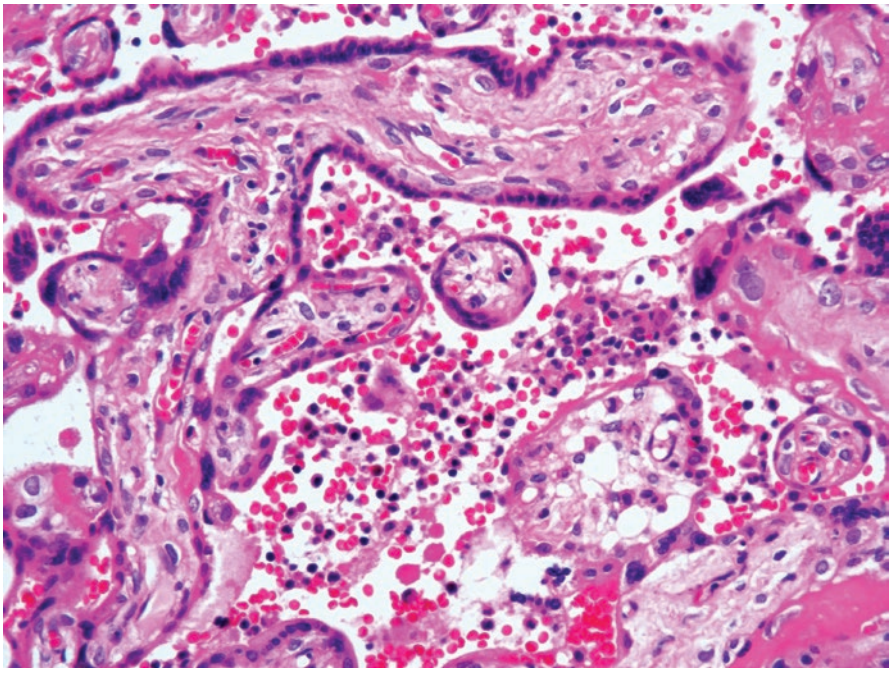

Fig. 23.16 Microscopic appearance of chronic histiocytic intervillositis. Many macrophages are present in the intervillous space

CHI produces no symptoms during pregnancy. Diagnosis is established exclusively postnatally on the basis of histology, but there is no final consensus on the diagnostic criteria. Heller [28] analyzed the CD68-positive cell count in CHI cases and control cases and found that the mean CD68 cell count per high-power field was 88 in the CHI cases and eight in the controls ($P < 0.01$). Capuani et al. [29] showed that, in CHI, inflammatory cells made up the predominant component (80%) of histiocytic cells apart from T cells (20%). The ratio of CD4 to CD8 cells was close to 1.

The frequent associations between VUE and CHI and the incidence of recurrence of both conditions make it difficult to establish a clear difference between the two. CHI is associated with a higher morbidity rate (intrauterine fetal death and IUGR) as compared to VUE, but the morbidity associated with combined lesions was similar to that of VUE.

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Part VII

Research Frontier

Genetic Analysis of Spontaneous Preterm Birth

24

Kenichiro Hata

Abstract

The studies show that genetic factors are partially involved in spontaneous preterm labor. However, most studies till date have not been successful in establishing a clear causal relationship between spontaneous preterm birth and genetic factors. The progress in recent high-throughput genomic analysis is expected to improve genetic analysis of premature birth. As a result, it has become possible to thoroughly analyze numerous spontaneous preterm labor cases and controls. Additionally, it is possible to target rare genetic variants and de novo mutations that have not been analyzed sufficiently in the past. In the future, detailed analysis will be performed after considering environmental factors such as the microbiome.

Keywords

Genetics · Genetic variants · GWAS · Novel mutation · Preterm birth · Rare polymorphism · SNP

24.1 Genetic Background of Spontaneous Preterm Birth

The studies suggest that incidences of spontaneous preterm birth accumulate in families, which are sometimes associated with epidemiologically racial differences. In addition, genetic factors of both mother and child, which are dependent on environmental factors and populations, affect birth [1]. The combined involvement of maternal and child genetic factors in determination of birth timing has been reported to be >30% [2]. According to heritability (inheritance of a genetic factor of a certain

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Table 24.1 Speculated heritability of multifactorial phenotypes

Disease	Proportion of heritability (%)
Age-related macular degeneration	50.0
Crohn's disease	20.0
Systemic lupus erythematosus	15.0
Type 2 diabetes	6.0
HDL cholesterol	5.2
Height	5.0
Early onset myocardial infarction	2.8
Fasting glucose	1.5
Spontaneous preterm birth	>30.0?

Modified from Refs. [2, 3]

phenotype) of known diseases, single genetic diseases generally exhibit high heritability (Table 24.1) [3]. In contrast, the speculated heritability of spontaneous preterm birth is not low compared to those of other hereditary (or suspected hereditary) diseases and phenotypes, as shown in Table 24.1. Therefore, methods of detecting "gene features" involved in spontaneous preterm birth should be developed.

The human genome project was completed in 2003, which involved an expenditure of $3 billion in 13 years. Thereafter, various genome analysis technologies have advanced rapidly in its wake. However, the human genome project was based on genomic data of only few individuals. Currently, further analyses are underway for understanding the diversity among ethnic groups and individuals, for example, correlation of phenotypic characteristics (genetic polymorphisms and/or mutations) with genetic sequences. The most interesting "phenotypes" for medical doctors are, of course, diseases, and variants and mutations in the causative genes of various diseases have been identified.

For example, the association between intrauterine infection and spontaneous preterm birth might have been advantageous for our ancestors because termination of pregnancy with minor signs of infection might prevent lethal complications of mothers during pregnancy. Therefore, "infection sensitive" genetic variations are not negatively selected in human evolution, but persist at a certain frequency. In fact, based on a similar hypothesis, the association between various single nucleotide polymorphisms (SNPs) and spontaneous preterm birth has also been reported [4].

24.2 Genetic Analysis of Spontaneous Preterm Birth Using Candidate Genes

Candidate gene association studies are examples of conventional genetic analyses. The candidate genes are selected from various prior studies on pathology, physiology, biochemical analysis, and gene mutation in related diseases, similar symptoms observed in model mouse, etc., whereas the selected gene functions were those that provided clues regarding molecular etiology. If an association between gene function and spontaneous preterm birth is suggested, the sequence of the gene is compared between the spontaneous preterm birth group and the normal delivery group, and alterations in the gene sequence specific to the spontaneous preterm birth group

(variants or mutations) are checked. Compared to comprehensive whole-genome analysis, genetic analysis of few candidates has the advantage of being low-cost, which will be explained later in this review. SNP association studies are examples of typical candidate gene analysis. Single base differences in a gene may change the amino acid composition and activity of the translated protein compared to that of the wild type (normal) protein. These changes might affect enzyme activity, expression, processing, and stability. Alternatively, variations and mutations in promoters, genetic elements that control gene expression, may change promoter function, resulting in changes in gene expression level (the amount of protein produced) without affecting protein structure. As a result, variants and mutations may weaken or strengthen the function of certain genes and cause diseases.

Based on this hypothesis, SNPs in genes encoding various cytokines, cytokine receptors, innate immune system factors, and matrix metalloproteinases, etc. were examined in cases of spontaneous preterm birth, and factors showing significant differences between the spontaneous preterm birth and normal delivery group were reported. However, in many cases, the results were not reproduced in the follow-up studies [5]. These discrepancies may be due to the fact that the classification of cases (stratification based on collected clinical information and examination values) was not identical in those reports and/or was affected by ethnicities and genetic backgrounds rather than inappropriate research design.

It is noteworthy that selection of candidate genes at the beginning of the study is a challenging task. The target cells/organs are known for most single gene disorders. Even for single gene disorders with ambiguous targets, one can usually infer the molecular pathology by detailed examination of the symptoms. Therefore, strategies for comparing disease and control groups after selection of candidate genes may work in many cases. For example, the symptoms and histopathological evidence in "sickle cell disease" clearly show that essential pathological conditions exist in erythrocytes, and therefore, the candidate genes can be narrowed down to erythrocyte biology-related genes. Therefore, what is the "essential lesion of spontaneous preterm birth"? Since most cases of spontaneous preterm birth are multifactorial diseases, the results obtained are limited even if they are obtained using a strategy similar to that used for single gene disorders. Classification based on epidemiological findings and clinical conditions of spontaneous preterm birth will be reviewed by other authors; however, from various viewpoints, classification of spontaneous preterm birth cases, and selection and collection of cases suspected to have identical molecular pathological background, will significantly improve the efficiency of genetic analysis.

24.3 Genome-Wide Association Studies of Spontaneous Preterm Birth

In the "candidate gene approach" mentioned above, known gene functions or upstream/downstream genes of the candidate genes are targeted. In other words, few research findings that new factors and/or molecular mechanisms that cannot be speculated at all can be found from the research results.

On the contrary, various high-throughput genome analysis methods have been developed based on the results of the human genome project, which are being improved continuously worldwide.

A genome-wide association study (GWAS) was first reported in 2002 by a Japanese research group, and several studies on genetic factor analysis of "common diseases" and "multifactorial diseases" such as diabetes and hypertension have been performed. GWAS has the potential to provide new findings without narrowing down the candidate factors in advance.

Unfortunately, GWAS has not yielded remarkable results in studies on spontaneous preterm birth. Although the reason is unknown, it has been speculated that the number of cases analyzed is relatively small, and classification of cases with similar molecular disease background was not successful.

Recently, the results of GWAS based on 43,568 large-scale genomic data were reported. The authors received genome data from 23andMe (a privately held personal genomics and biotechnology company co-founded by Anne Wojcicki) and analyzed 37,803 cases of regular term outbreaks, 3331 spontaneous preterm births, and 2432 cases of overtime production [6]. As a result, *EBF1* (B lymphocyte-related gene), *EEFSEC* (gene involved in selenoprotein production), and *AGTR2* (encoding angiotensin receptor) were identified as genes involved in the gestation period. At the first glance, it is difficult to infer the direct causal relationship between these genes and spontaneous preterm birth. Identification of unexpected and unknown factors is one of the advantages of using GWAS. However, it is necessary to identify the molecular mechanisms to understand why dysfunction of these genes causes spontaneous preterm birth in the future. In addition, the effect of other genetic backgrounds such as Asian ethnicity (this research was a genome-wide association study conducted on European-origin women) should be confirmed before speculating on the molecular epidemiology of the disease.

24.4 Analysis of Rare Polymorphisms and Novel Mutations

As has been already mentioned, unlike studies based on speculated molecular pathways of diseases or candidate genes, GWAS can detect unexpected etiological candidate genes. Conventional GWAS is based on known genetic polymorphisms present in the normal population at a certain frequency. Therefore, all phenotypes cannot be explained using conventional GWAS, as it does not contain the less frequent genetic variants or de novo mutations.

In fact, even if the existing GWAS data are compiled, many diseases that do not show the estimated heritability will be excluded, a contradiction termed "missing heritability." The main reasons why "missing heritability" is observed are as follows: (1) The variants currently used for GWAS are not sufficient. For example, insertion/deletion variants and rare variants that are several kilobases in size are difficult to identify using the current standard analytical methods, and are excluded from GWAS. (2) Although it is possible to explain most diseases with conventional GWAS using only current frequency information of common variants, the

etiological gene is not detected because of small sample size. (3) The cited heritability predicted from familial case data is large. Recently, two studies used whole-genome sequencing data from the UK large-scale biobank (UK Biobank). In one of these studies, Yang et al. showed that even the variants currently used for GWAS could predict the genetic factors of most diseases if the sample size was sufficient [7]. In addition, Muñoz and colleagues concluded that estimated heritability with simple family-based statistical models is overestimated [8].

Sequence analysis using next generation sequencing is often performed to search for candidate genes associated with single genetic diseases. This is because we can identify rare polymorphisms and unknown sequence changes (de novo mutations and insertion–deletion mutations) using next generation sequencing. This is fundamentally different from GWAS, which uses only known polymorphisms.

A recent study reported the result of analyzing 76 cases of premature rupture of membranes (PROM) using next generation sequencing [9]. The results showed that genes such as *DEFB1* (encoding defensin), *MBL2* (encoding lectin binding protein), and *TLR10* (encoding toll-like receptor [10]) harbor rare polymorphisms not observed in women who delivered normally. These putative pathogenesis-associated genes identified in this study encoded several factors such as the inflammasome, which is involved in innate immunity. Inflammasome-related factors are known to form complexes with multiple proteins and participate in various autoimmune and inflammatory diseases. Abnormalities in the constitutive factors of these complexes affect downstream events and cause abnormal inflammatory reaction. In addition, abnormalities in the complex or factors with varying mutations in the complex might affect the downstream events slightly differently, possibly leading to different clinical manifestations. However, it is difficult to observe and stratify subtle differences in clinical phenotypes of these cases, and identify these genetic polymorphisms using conventional GWAS. In the future, advancements in the identification of "de novo mutations and rare polymorphisms" using such analytical methods are expected.

24.5 Future Prospects

Genomic analysis has not always been able to yield remarkable results from preliminary laboratory research. Therefore, the question arises as to whether continuance of genome analysis of premature birth is required.

Of course, new ideas for compensating the lapses in previous reports of spontaneous preterm birth are necessary. For example, knowledge regarding the contribution of environmental factors and genetic background is important. Recently, we performed detailed microbiome analysis of spontaneous preterm birth cases and proposed new classification and diagnostic methods [10]. We should introduce such new knowledge positively and devise measures of stratifying preterm birth in addition to conventional clinical, pathological, and biochemical observations.

Nevertheless, even after other groups reported genetic studies of preterm birth, such as GWAS, reanalysis with respect to different ethnicities and genetic

backgrounds did not yield conclusive results. For example, numerous GWAS results are available for diabetes, but reanalysis in a Japanese group revealed a new related gene that was missed because of its low frequency in European individuals [11].

In conclusion, GWAS is an analytical strategy that has been developed to identify multifactorial diseases caused by interactions between environmental and genetic factors. Therefore, while GWAS requires large number of cases, strongly influential candidate genes are difficult to detect. In contrast, processing of large number of samples for next generation sequencing is laborious, although insertion–deletion mutations encompassing several kilobases, rare SNPs, and novel mutations can be targeted. The overlooked genetic factors will be identified by revalidation using these new methods.

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