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Current therapeutic strategies to prevent preterm birth

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ABSTRACT

Premature birth (PTB) is one of the major causes of infant morbidity and mortality worldwide. Therefore, an effective prevention method is understanding the pathogenic processes that lead to PTB and identifying women at high risk. The purpose of this article is to review the most important prevention and therapeutic strategies for preterm birth. Thus, removing modifiable risk factors, the treatment or stabilization of maternal diseases that associate an increased risk of PTB, the treatment of infections are preventive strategies to reduce PTB. From a therapeutic point of view, the administration of tocolysis, corticotherapy, and antibiotic therapy are key points in the management of PTB to reduce neonatal sequelae and mortality due to prematurity.

Keywords: preterm birth, prematurity, prevention, therapeutic strategies

INTRODUCTION

Prematurity is the birth that takes place before 37 weeks of gestation [1]. The rate of premature births is estimated at 11% worldwide, with an average of 15 million premature babies born each year [2]. The highest rate of premature births is about 84% and occurs between 32 and 36 weeks of pregnancy, while between 28 and 32 weeks of pregnancy, the rate is about 10%, and only 5% is reported at gestational ages under 28 weeks. Premature birth is one of the most important causes of neonatal mortality, being found in about 50% of premature babies born before 25 weeks of pregnancy [3].

Current knowledge shows four pathogenic factors involved in the occurrence of premature birth: decidual hemorrhage, uterine distension, infection with inflammatory response, and activation of the maternal or fetal hypothalamic-pituitary-adrenal axis [4]. In women with a history of premature birth, cervical surgery, and a short ultrasound cervix (< 25 mm), there is a high risk of premature birth. The most important risk factor for preterm birth is the personal history of spontaneous preterm birth, with recurrence often occurring at the same gestational age [5].

Risk factors for preterm birth are related to the mother and include associated diseases (systemic infections, sexually transmitted infections), uterine factors (uterine malformations, a history of cervical surgery, cervico-isthmic incontinence, leiomyomas), and lifestyle factors (low body mass index, low educational level, stress, smoking, maternal age under 16 or over 35 years). Fetal factors are represented by multiple pregnancies, fetal birth defects, fetal anemia, growth restriction. Other factors are polyhydramnios, placental abruption, placenta praevia [6].

Premature birth involves both short-term and long-term fetal complications. In the short term, respiratory complications (respiratory distress syndrome), gastrointestinal (ulceronecrotic enterocolitis), neurological (convulsions, cerebral palsy, in-

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traventricular hemorrhage, periventricular leukomalacia, ischemic hypoxic encephalopathy), or sepsis may occur. Long-term complications include poor outcome development, behavioral disorders, and learning difficulties [3,7]. Interventions to reduce the risk of premature birth depend mainly on risk factors and the reproductive history of the pregnant woman [8].

Understanding the pathogenic processes that lead to PTB and the development of new therapeutic and preventive interventions can significantly reduce the rate of PTB.

PREVENTIVE STRATEGIES TO REDUCE THE RISK OF PRETERM BIRTH

Premature labor has a multifactorial etiology, and identifying the modifiable risk factors for PTB early during pregnancy or before conception can help develop a preventive strategy. Among the potentially modifiable risk factors, nutritional supplementation with calcium, iron, folic acid, zinc, and other elements reduces the risk of premature birth below 34 weeks. Quitting smoking also reduces this risk. In addition, prophylactic administration of aspirin before 16 weeks reduces the risk of premature birth in women at high risk of preeclampsia [8,9].

Infection is the causative factor in up to 40% of premature births. Abnormal flora during pregnancy, both the genital tract and the oral cavity, is associated with premature birth. Pregnant women with periodontitis have a doubled risk of premature birth [10,11]. On the other hand, when bacterial vaginosis (BV) is diagnosed before 16 weeks of gestation, the risk of PTB is 5 to 7 times higher, persisting even when the microflora of the genital tract returns to normal. The therapeutic strategy for women with asymptomatic BV and without other risk factors for PTB is less well established, with little or no effect of antibiotic treatment on pregnancy prolongation.

In contrast, women with BV and history of PTB may benefit from screening and treatment for BV. However, there is no evidence that screening and treatment of asymptomatic Trichomonas infection in HIV-negative women reduces the risk of PTB. As a result, treatment of asymptomatic Trichomonas infection during pregnancy is recommended only for HIV-positive women. There is also no evidence that treatment of chlamydia, gonorrhea, or syphilis infections prolongs pregnancy, but treatment is recommended to prevent maternal and neonatal sequelae [12,13].

The administration of antibiotics to prevent or postpone childbirth in patients with premature labor and intact membranes is not beneficial, on the contrary, it can affect the microbiome and cause resistance to maternal antibiotics, necrotizing enterocolitis, cerebral palsy, antibiotic-resistant neonatal sepsis. In women with premature rupture of membranes (PPROM), antibiotic therapy is administered to treat the infection involved in the etiopathogenesis of membrane rupture, as well as for tocolytic purposes [4,14].

It is estimated that screening and treatment of bacteriuria in pregnancy are associated with a reduction in the incidence of prematurity and low birth weight by 20 to 50 percent and a reduction in the neonatal mortality rate by 5 to 14 percent [15]. All pregnant women should undergo a first-trimester urine culture. Those with a positive urine culture should be treated, and the urine culture should be repeated a week later and afterward monthly until delivery [16]. Regular antenatal screening for urinary tract infection is necessary only for those women at high risk for asymptomatic bacteriuria, such as sickle cell disease, recurrent urinary tract infections, diabetes mellitus, underlying renal disease, or prior PTB [17]. Pregnant women who have had a urinary tract infection during pregnancy are twice as likely to develop premature labor [18].

The interpregnancy interval can also influence the risk of preterm labor. A shortened interpregnancy interval, usually considered below 18 months, is linked to a greater risk of adverse perinatal outcomes. Women who conceive sooner than 6 months after the previous birth have a three-fold higher risk of preterm birth at less than 34 weeks of gestation, premature rupture of membranes, small for gestational age (SGA) infants, or fetal demise [19,20,21]. The risk persisted even when the previous delivery was at term [22]. Therefore most studies recommend an interpregnancy interval of more than 12 months, but no more than 60 months to prevent poor prognosis of pregnancy [19,23,24].

Progesterone supplementation for well-selected high-risk women may be effective as a therapeutic strategy to reduce the risk of preterm birth [25,26]. Progesterone is produced until 9 weeks of gestation by the corpus luteum and afterward by the placenta. It is essential for pregnancy maintenance. As a result, administering a progesterone antagonist or removing the corpus luteum before 7 weeks of gestation induces abortion [27]. The appropriate selection of the patients is very important. Data available from studies suggest that progesterone supplementation has a beneficial effect in the following settings: women with a singleton or twin pregnancy and a past history of spontaneous preterm birth, women with a singleton or twin pregnancy and short cervix (≤ 20 mm) demonstrated by transvaginal ultrasound [28]. The dose, route of administration, and type of progestin have a great impact on the efficacy of the treatment. For those women with

a prior history of PTB most studies recommend hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning at 16-20 weeks of gestation and continuing until 36 weeks of gestation or until delivery [29,30]. Natural progesterone administered vaginally is an alternative treatment. Studies recommend administering a 100 mg micronized progesterone vaginal tablet or an 8 percent vaginal gel containing 90 mg micronized progesterone per dose for women with a short cervix, from the time of diagnosis until 36 weeks of gestation [25]. Progesterone supplementation has an unclear effect in the following settings: women with a prior preterm birth after the placement of a cerclage, women with a positive fetal fibronectin test, women who remain undelivered after an episode of threatened preterm labor, women with uterine malformations or who conceive with assisted reproductive technology, maternal obesity. Therefore, studies do not recommend routinely progesterone supplementation in these situations [31-34]. Vaginal progesterone improves outcomes in neonates and significantly decreases neonatal morbidity and mortality, low weight at birth, and NICU admission. Current data should reassure medical professionals that vaginal progesterone is effective and safe for reducing the incidence of preterm birth in the selected category of pregnant women [35].

Uterine malformations occur in approximately 5% of women of reproductive age, in 5-25% of women with the adverse perinatal outcome, and are associated with an increased risk of preterm birth [36,37]. The most frequent uterine malformation in women with adverse reproductive outcomes is a septated uterus [38], while the most frequent uterine malformation in the general population is the arcuate uterus [39]. Surgical treatment of unicornuate, septated, or bicornuate uterus is associated with an improvement in fetal survival and obstetrical outcomes, especially for those patients with a prior history of recurrent abortion or infertility. However, it is not established whether surgical management of uterine malformations positively impacts the preterm birth rate [40].

There is an association between uterine fibroids and the risk of PTB [41,42]. Studies report an increased risk of preterm birth in the following settings: fibroids greater than 5 cm or multiple fibroids, placenta adjacent to or overlying the fibroid [43]. The size of fibroids does not change during pregnancy in most cases, but still, in the first trimester, there may be an increase to one-third of them. This growth is faster until mid-pregnancy, reaches its peak in the first trimester, and stabilizes or even regresses [44]. Pre-pregnancy myomectomy may improve pregnancy outcomes in women with large or rapidly growing intramural fibroids (> 5 cm), with type 0 and type 1 submucosal fibroids, and a history of recurrent pregnancy loss without other etiology [45,46].

Cervical insufficiency is a significant risk factor for preterm birth. Several factors lead to cervical insufficiencies, such as connective tissue disorders, uterine malformations, cervical trauma, rapid mechanical cervical dilatation, and conization [47,48]. Most patients have no symptoms and are diagnosed accidentally during the ultrasound surveillance. Other women have abdominal pain or pressure symptoms and/or a change in the volume, color, or consistency of vaginal discharge [47]. At 12 to 14 weeks, transvaginal cerclage is indicated for women with ≥ 2 consecutive prior second-trimester abortions, or ≥ 3 at less than 34 weeks of gestation preterm births. Transabdominal cerclage may be indicated for those women with a prior preterm birth at less than 33 weeks of gestation after the placement of a transvaginal cerclage [49,50,51]. Studies recommend serial measurement of cervical length at 16 weeks and ending at 24 weeks for those patients with one prior second-trimester abortion or one or two preterm births. If the cervical length is less than 25 mm before 24 weeks of gestation, the placement of a transvaginal cerclage is indicated [52,53]. Those women with risk factors for cervical insufficiency without a prior history of PTB or second-trimester abortion are surveyed with serial measurement of cervical length beginning at 18 weeks until 24 weeks of gestation, and the placement of a transvaginal cerclage is indicated if the cervical length is less than 20 mm [54].

Other preventive strategies include treating chronic maternal medical disorders or reducing multifetal gestations in pregnancies conceived by assisted reproduction techniques [55,56]. Surgical uterine evacuation appears to be associated with a small but statistically significant increase in the risk of PTB, on the other hand, medical abortion has no impact on future pregnancies [57].

TREATMENT OF PRETERM LABOUR

All women who present with preterm labor should be evaluated using the following laboratory tests: a rectovaginal group B streptococcal culture if not done within the previous five weeks, urine culture, tests for sexually transmitted diseases (taking into account the patient's risk factors for these infections), fetal fibronectin for pregnancies < 34 weeks of gestation with cervical dilation < 3 cm and cervical length 20 to 30 mm on transvaginal ultrasound examination [58]. A 50 ng/ml fibronectin concentration in the cervicovaginal fluid between 22 and 34 weeks of gestation is associated with an increased risk of preterm birth in the following 7 days [59,60].

Tocolytic therapy can reduce the risk of PTB, and the purpose of its use is to delay birth by at least 48 hours. Tocolytics are indicated for pregnancies between 22 and 34 weeks of gestation. It is less useful when the cervical dilation is greater than 3 cm. There are several contraindications to administering tocolytic drugs, such as fetal death, nonreassuring fetal status, chorioamnionitis, maternal hemodynamic instability due to hemorrhage, preeclampsia, or severe eclampsia [61,62].

Indomethacin can be used for tocolysis at 24 to 32 weeks of gestation for no more than 48 hours. The loading dose is 50 to 100 mg, followed by 25 mg orally every four to six hours. Maternal contraindications to indomethacin include gastrointestinal ulcer, renal or liver insufficiency, bleeding diathesis, and asthma. In addition, the administration of indomethacin is contraindicated after 32 weeks of gestation because it increases the risk of fetal ductus arteriosus constriction and oligohydramnios [61].

Nifedipine is a first-line tocolytic agent and can be used for the treatment of those women who do not respond or have contraindications to indomethacin. Adverse effects of nifedipine include hypotension, nausea, flushing, headache, and palpitations. The initial loading dose is 20 to 30 mg orally, followed by a dose of 10 to 20 mg orally every 3 to 8 hours for up to 48 hours. The maximum accepted dose is 180 mg/day [61,63]. Studies support using calcium channel blockers as short-term tocolytics over other available agents because of their relatively greater contraction suppression and fewer side effects than other agents [64].

Beta-2 receptor agonists cause smooth muscle relaxation, the myometrium being made of this type of fiber. Terbutaline and ritodrine are the most commonly used beta-agonist for tocolysis. Maternal side effects occur quite frequently and include tachycardia, palpitations, hypotension, cardiac arrhythmias, tremor, and chest discomfort, and in rare cases can cause pulmonary edema. They also have metabolic effects, such as hypokalemia and hyperglycemia. It must not be used in women with bleeding, heart disease, poorly controlled hyperthyroidism, diabetes, renal or hepatic impairment [61,65]. Beta-agonists cross the placenta and can cause fetal tachycardia, hyperglycemia, and hyperinsulinism. Exposure in utero gives an increased risk of autism or asthma in childhood [4,61]. Due to their significant side effects and reduced efficacy compared to other tocolytic agents, betamimetics are not recommended with the first intention of inhibiting labor [4].

Atosiban is a selective oxytocin-vasopressin receptor antagonist and inhibits spontaneous and oxytocin-induced contractions. It can also interfere with prostaglandin F (PGF2α) signaling pathways in initiating and maintaining labor. It can significantly reduce uterine contractions and thus delay premature labor, prolonging pregnancy by at least 48 hours. It is considered a superior tocolytic agent to the other classes due to insignificant maternal and fetal side effects. The main maternal side effects are hypersensitivity, injection site reactions, headache, hypotension, chest pain, nausea, vomiting. Although it crosses the placenta, no fetal side effects have been reported [4,61,66].

There are currently clinical trials for novel tocolytic agents, such as the reversible prostaglandin F 2-alpha receptor inhibitor (PGF2α) (OBE-022), interleukin 1 receptor antagonists, and nanoparticles [4].

TREATMENTS TO REDUCE THE MORBIDITY AND MORTALITY OF THE NEWBORN

Magnesium sulfate can act in premature birth both as a tocolytic agent and as a neuroprotector for the newborn by regulating calcium absorption, including uterine tissue. In the case of premature births before 32 weeks of gestation, it reduces cerebral palsy by 55% at 2 years if it is administered 24 hours before birth [61,67]. The dose used for neuroprotective purposes is 4g in 20 minutes intravenously the loading dose, followed by a maintenance dose of 1g / hour, for 24 hours, monitoring diuresis and maternal osteo-tendinous reflexes. Maternal side effects include blurred vision, gastrointestinal upset, erythema, lethargy, respiratory arrest, and pulmonary edema. Co-administration of calcium channel blockers or beta-agonists due to worsening side effects is not recommended [4,68]. Following administration of magnesium sulfate, the newborn may experience lethargy and prolongation until the onset of stable breathing. Also, long-term administration is not recommended because it crosses the placenta and can cause fetal hypermagnesemia with hypocalcemia and osteopenia [4].

All pregnant women should be tested for group B Streptococcus (GBS) infection at 35 to 37 weeks of gestation. Antibioprophylaxis is recommended in the following situations: GBS bacteriuria during the current pregnancy, prior history of an infant affected by GBS disease, positive vaginal or rectal culture for GBS. It is also indicated for women with an unknown status of GBS who present with intrapartum fever, delivery before 37 weeks of gestation or after 18 hours of ruptured membranes [69].

Antenatal treatment with glucocorticoids reduces perinatal mortality and morbidity caused by respiratory distress syndrome (RDS) or intraventricular hemorrhage (IVH). Studies support the administration of antenatal corticosteroids for all women from 24 to 34 weeks of gestation who have a high risk of PTB within the next seven days. The

use of corticosteroids after 34 weeks of gestation remains unclear. Therapeutic options include a 48-hour course of dexamethasone (4 doses of 6 mg given intramuscularly every 12 hours) or a 24-hour course of betamethasone (2 doses of 12 mg given intramuscularly every 12 hours) [62]. Administration of antenatal corticosteroids may be associated with transient low biophysical profile score, which persists no longer than 2 or 3 days. They can also cause maternal hyperglycemia, the elevation of the leukocyte count, and increase the risk of chorioamnionitis or endometritis in patients with premature rupture of membranes [70].

CONCLUSIONS

PTB is a multifactorial obstetric problem with important implications for neonatal morbidity and mortality. The prompt identification and elimination of risk factors associated with premature birth and the choice of the most effective specific treatment allow the postponement of birth, with reduced maternal and neonatal side effects.

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