Prediction and prevention of spontaneous preterm birth

Predição e prevenção do parto pré-termo espontâneo

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ABSTRACT

Incidence of preterm delivery ranges from 7-12% of all gestations and premature birth is one of the main causes for newborn morbimortality. It is responsible for over three quarters of neonatal deaths, minus congenital malformations. Several strategies can be adopted to reduce premature delivery rates, including risk factor identification and prophylactic use of progesterone. Among the main actions of progesterone is its relaxing effect upon uterine muscles, the ability to block the effects of cytokin, and its anti-inflammatory and immunosuppresive effects. The use of exogenous progesterone reduces the rates of prematurity for patients under risk of premature delivery, such as those with a history of premature deliveries, and short cervix as revealed by transvaginal ultrasound in the second quarter of pregnancy. This review aims to highlight important aspects to be considered in the outpatient clinic and describe the main predictive and preventive actions of premature birth available in obstetric care.

Key words: Premature Birth/prevention & control; Obstetric Labor, Premature; Infant Mortality.

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RESUMO

A incidência de parto pré-termo varia de 7-12% de todas as gestações e o nascimento prematuro é das principais causas de morbimortalidade neonatal, responsável por mais de três quartos das mortes neonatais, quando malformações congênitas são excluídas. Várias estratégias são adotadas com o objetivo de reduzir as taxas de partos prematuros, incluindo a identificação de fatores de risco e o uso profilático de progesterona. Destacam-se, entre as principais ações da progesterona, o efeito relaxante sobre a musculatura uterina, a capacidade de bloquear os efeitos da ocitocina, o efeito anti-inflamatório e imunossupressor. O uso de progesterona exógena reduz as taxas de prematuridade em pacientes com risco de parto prematuro, tal como história prévia de parto prematuro, e colo uterino curto demonstrado pela ultrassonografia transvaginal no segundo trimestre de gestação. Esta revisão objetiva, inicialmente, evidenciar aspectos importantes a serem abordados na assistência ambulatorial e, posteriormente descrever as principais ações preditivas e preventivas do nascimento prematuro disponíveis na assistência obstétrica.

Palavras-chave: Nascimento Prematuro/prevenção & controle; Trabalho de Parto Prematuro; Mortalidade Infantil.

INTRODUCTION

Preterm birth is one of the biggest challenges in contemporary medical practice, featuring as the main cause of neonatal morbidity and mortality all over the world. Its influence is also relevant to general health care because of long-term sequelae, such as alterations in neural development and higher risk of chronic diseases in adults.[1]

A birth is considered preterm when it takes place before a 37-week gestation is completed and it can be either spontaneous or, in most cases, therapeutically induced by a physician (or iatrogenic) due to maternal and/or fetal complications. It is associated respectively[2] with preterm labor and preterm premature amniorrhexis, or with the physician's indication to bring the pregnancy to term due to clinical complications that might jeopardize the mother's or the fetus' health. Examples of such complications include intrauterine growth restriction, pre-eclampsia, placent previa, non-reassuring fetal status, or placental abruption.

Births can be classified according to gestational age[3] at birth: extremely preterm (from viability [20-22 weeks] to 28 weeks), very preterm (28 to 32 weeks), and moderate preterm (32 to 37 incomplete weeks). A late preterm birth is that which occurs after the 34th gestational week. Considering birth weight, a newborn can be[4]: underweight (< 2,500 g), very underweight (< 1,500g), or extremely underweight (<1,000g). Both classifications are relevant because they influence the outcome of long-term neonatal morbimortality and sequelae.

IMPORTANT ASPECTS OF PRETERM BIRTH

Prematurity and its serious consequences are a complex health care problem that stands as the main cause of neonatal morbimortality.

It is hard to accurately measure occurrences of preterm birth. Few countries have reliable data about this obstetric event and several factors influence its occurrence: the population's education levels, quality of prenatal care, characteristics of the institution carrying out the research, the conceptualization of preterm birth, and the subdivision into spontaneous or induced.

There is a high occurrence of preterm births in underdeveloped countries. Around the world, the average preterm birth rate is 11%, from 5% in Europe to 18% in Africa. Approximately 15 millions children are born prematurely every year. Among preterm births, 84%, 10% and 5% occur between 32 and 36, 28 and 32, and before 28 weeks respectively.[3,5]

In the United States, occurrences of prematurity have increased in recent years from 9.5% in 1981 to 12.7% in 2005.[6] Paradoxically, part of this increase is accounted for by technological progress in medical care. More accurate maternal and fetal state diagnoses can cause induced preterm birth to be recommended, and assisted reproductive technology has led to an increase in occurrences of multiple pregnancies and advanced maternal age. Improvements in neonatal care in Brazil mean that early interruptions in cases of relative indication are no longer discouraged.

Prematurity rates in Brazil were at 6.6% in 2006 and have been stable since 2001 (6.3%). These data must be interpreted with caution. Underrporting can occur as a result of the difficulty in obtaining confirmation of gestational age through ultrasonography, a reality with which many parts of the country still struggle. Data analysis regarding birth weight showed that in 2006 8.2% of the 2,994,928 live births recorded in Brazil weighed under 2,500g (no distinction between prematurity and IUGR), amounting to 241,606 newborns. In 1994, the rate was 7.4%.[7]

Prematurity in Brazil saw an increase of 3.4% in preterm births between 1978 and 2004 in the South and Southwest regions respectively. In the Northeast, these rates range from 3.8 to 10.2% between 1984 and 1998 respectively.[8]

PREDICTING PRETERM BIRTH

Premature birth is classically considered to have unknown etiology in 50% of cases, but there often is an association between maternal and fetal risks that can be classified as: epidemiological, gynecological, clinical-surgical, genetic, iatrogenic, and unknown.

Prenatal care

Attempts to predict premature birth have been made through analysis of several parameters, such as: clinical history, maternal age (below 18 and above 35), habits (smoking, alcohol consumption, and use of illegal drugs), social background (stressful event, excessive workload), OB/GYN history (parity, previous abortions, a history suggestive of cervical insufficiency, leiomyomas and uterine malformations). It is important to accurately determine the gestational age of any previous premature deliveries to establish a predisposition to preterm delivery; diagnosis of vaginitis and UTI through cultures and Gram stains; identification of biochemical markers, such as fetal fibronectin (fFN) in the vaginal contents, or the insuline-like growth factor (pHIGFBP-1); short cervix assessment through transvaginal ultrasound; gaug-

ing of excessive uterine contractions with cardiotoco-graphic monitoring.[9-11]

Vaginal infection assays

Pregnant women with a risk of premature delivery also require, besides oncotic colpocitology, bacteriological examination and microbiological culture of vaginal contents in the first prenatal care appointment and once again in the last three months. Specific treatments must be pursued in face of the following agents: Gardnerella vaginalis, Mobiluncus sp., Bacterioides sp., Mycoplasma hominis, Trichomonas vaginalis, Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasma urealitycum and Treponema pallidum, among others. Bacterial vaginosis can be diagnosed in case of lactobacilli reduction or presence of clue cells in microscopy analysis (Gram) or through bacterioscopy and culture showing Gardnerella vaginalis, Mobiluncus sp., Bacterioides sp., Mycoplasma hominis. Bacterial vaginosis can be known if vaginal pH is equal or less than five or if ammonia can be smelled after contact with a potassium hydroxide solution.

If group B streptococcus is found in the vaginal contents or urine at any stage of gestation, even if treatment is pursued during the gestation, profilaxis is mandatory throughout labor in order to prevent vertical transmission and lessen the risk of neonatal infection.

Monitoring uterine contractions

During labor, be it term or preterm, contractions progressively grow in intensity and frequency, causing repercussions to the cervix, such as shortening, dilation, amniotic sac formation, and fetal head descent.[12]

Cardiotocography is a method that records uterine activity. Although monitoring uterine contractions is not a good method for tracing premature delivery, when dealing with high-risk patients reporting pelvic pain it can corroborate the diagnosis or rule out labor and/or uterine irritability, thus allowing the use of suitable therapy or avoiding unnecessary measures, such as tocolytics or corticosteroid therapy.

Due to the high rate of false-positives, if an increase in uterine contractions is diagnosed, the test must be compared with other markers and previous examinations in order to avoid misconduct.

Fetal fibronectin (fFN) and other biochemical markers

Certain biochemical markers are used in the analysis for predicting preterm delivery, among them: corticotropin-releasing hormones in the mother's serum and blood, salivary estrogen, serum collagenase, cervicovaginal cytokines, granolucyte elastase, and fetal fibronectin.[13]

Fetal fibronectin (fFN) is the most frequently used biochemical marker as part of preterm delivery prediction. It is a glycoprotein produced by the trophoblast. Normally, fFN is present in the vaginal contents during the first 20 weeks of gestation. After the 22nd week, a complete fusion occurs between the amniotic sac and the chorion and fFN is no longer be present in the vaginal contents until labor is approaching. Between the 22nd and 36th week of gestation, fFN in the vaginal contents can be associated with local inflammatory and/or infectious processes, with ischemic processes in the chorion-decidual interface and premature rupture of membranes. It such situations, it behaves as a premature delivery prediction marker, and assay is advised for risk pregnancies and as an aid to diagnosing premature labor.[14,15]

Another marker that can be checked in vaginal contents is insuline-like growth factor-I, (pHIGFBP-1), (phIGFBP-1), a protein secreted by the decidua and found in vaginal discharge near the time labor.[11]

Although the use of both markers is promising, particularly in symptomatic patients who require false premature labor to be excluded, its use in Brazil is still restricted to research centers. More widespread use ought to be considered by government agencies as it would allow for more effective action in symptomatic patients in the public health care sphere. This would certainly lessen hospital and transport-related expenses and, above all, prevent unnecessary relocations from cities that lack hospital infrastructure to places with available tertiary health care.

Cervical length assessment

Serial endovaginal sonography can reveal changes in the cervix and in the amniotic membranes. This is a big breakthrough in preterm birth prevention.

The risk of preterm birth increases progressively as the cervix becomes shorter. Patients between 20

and 24 weeks have an increased risk of preterm birth when their cervical length is below 2.5cm.[16]

Ultrasound screening for risk of premature birth is not recommended for patients showing no risk factors or patients before the 16th week, in which cases it is of little value as it is difficult to distinguish the portion of the cervix.

Other markers made evident through ultrasound can be associated with cervical length to predict preterm birth. Funneling of the amniotic membrane corresponds to the effacement of the cervix, which entails a decrease in cervical length. Loss of the glandular region of the cervix is part of the cervix maturation process and suggests an increased risk of preterm birth. Another parameter that should be mentioned is amniotic "sludge", a lymphocitary infiltrate that indicates intracavitary infection, which could lead to preterm birth.[16]

Twin pregnancy is an important risk factor for preterm birth. However, performing an endovaginal sonography in this case has low positive predictive value for preterm birth. No kind of intervention, including cervical cerclage and progesterone supplementation, has proved beneficial in multiple gestations or short cervix.[17,18]

PRETERM BIRTH PREVENTION

So as to reduce preterm birth rates, one must consider eliminating risk factors as well as using potentially effective interventions directly related to prevention. Identifying risk factors of preterm birth before it happens, or even at the beginning of gestation, offers the opportunity for intervention so this outcome can be prevented. However, many preterm births occur in women without identifiable risk factors, which makes the use of preventive measures difficult. To attempt a prevention of preterm births by elimination of risk factors, the following must be attempted: to ensure an interval between pregnancies of ideally 18 to 24 months[19]; to diagnose and intervene in cases suggesting cervical incompetence and short cervix; to identify and treat uterine fibroids and maintain rigorous prenatal follow-up for multiple gestations; to research and treat asymptomatic bacteriuria, genital infection and periodontal diseases; to drain polyhydramnios, when needed; to adjust intensity of exercise and work;[20] to ban smoking and consumption of alcohol and drugs;[21] to reduce sexual activity in specific cases; and to use condoms.

There is evidence that cerclage can reduce the risk of recurrent preterm births and miscarriage when dealing with a past medical history of cervical dilation, even if there are no contractions or direct causes for labor, such as an infection.

Diagnosis of cervical incompetence can be reached through careful investigation and includes obstetric history of late miscarriages - from 14 weeks of gestation, with elimination of a living fetus, without previous bleeding. It also encompasses early preterm births - before the 26th week, with no identification of uterine activity. Normally, these are recurrent pregnancy losses. In the cases of typical history, the characteristics of the cervix during an ongoing pregnancy, such as effacement and sonographic measurement of length, are of little value.

Cerclage must be performed preferably between the 12th and 16th gestational weeks, as soon as the phase when chromosome abnormalities feature as a cause of spontaneous abortions comes to an end. It is then early enough to interfere positively in the continuity of the gestation by correcting cervical incompetence.

PROGESTERONE AND PREVENTION OF SPONTANEOUS PRETERM BIRTH

Progesterone is a steroid hormone with an essential role in keeping up an early pregnancy. It is produced by the corpus luteum until the placenta takes over this function, around the 7th or 9th week. As evidence of this role, removal of the corpus luteum (progesterone source) or use of a progesterone receptor antagonist leads to abortion before the 7th gestational week.

The role of progesterone in later stages is unclear. It seems important in the upkeep of uterine quiescence in the second half of gestation, possibly by limiting production of prostaglandins and inhibiting the gene expression of proteins associated with myometrial contractions. It also acts by inhibiting ion channels, oxytocin receptors, prostaglandins, and gap junctions, causing smooth muscles to relax and blocking uterine activity.[22,23]

Although progesterone levels in maternal circulation do not undergo significant alterations in the weeks preceding labor, this hormone's functions in the uterus attenuate at that moment.[24]

Progesterone prevents apoptosis in the fetal membrane in both basal and pro-inflammatory conditions. This seems to prevent preterm early rupture of membranes, a common cause of preterm birth.

These observations give us the basis on which to use progesterone supplementation for preventing preterm birth.[25-27] Current recommendation consists of using intravaginal progesterone supplementation, beginning in the 16th week up to the 34th or 36th gestational weeks, in the cases discussed below. It must be applied at night during bedtime to avoid loss of medication to orthostatism. Based on obstetric history, progesterone is indicated in cases of previous preterm birth.[28]Use of progesterone is not possible in case of amniorrhexis or in ongoing labor.[29,30]

Progesterone is also useful for patients with short cervical length as shown by sonography (below 25mm), reducing occurrences of prematurity below 33, 34, and 35 gestational weeks.[31,32]

Risk of preterm birth[33] below 32 weeks is closely related to cervical length measured between 20 and 24 gestational weeks: 0.2% if cervical length is 6.0cm, up to 78% if cervical length is 0.5cm.

The benefits of progesterone for twin pregnancies have not been established, probably because the labor triggering mechanism in these cases relates more to increased uterine distension than to progestongenic imbalance.[17]

CONCLUSIONS

Based on the medical, social, and economic consequences of preterm birth, and considering that the main cause of prematurity is spontaneous birth,[4] preventing it is an imperative task on prenatal care, as well as any other levels of care to the pregnant mother.

Many questions still exist regarding the etiology and pathophysiology of preterm birth, but a complete medical history is the first step toward reducing prematurity rates by identifying risk factors and thereby acting on those that can be reverted. Further investigation with ultrasound and biochemical testing must be performed so that preventive action cans be implemented.

Progesterone constitutes a very good option to prematurity prevention in carefully selected patients.

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