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REVIEW ARTICLE

Predictors of preterm birth

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Abstract

Objective: This is a systematic review to assess published scientific evidence on preterm birth predictors. *Methods*: An Internet search for predictors of preterm birth was performed and the evidence level of each method was evaluated. *Results*: There is strong evidence that preterm birth can be predicted using vaginal sonography to evaluate cervical characteristics, fetal fibronectin in cervicovaginal secretions and interleukin-6 in amniotic fluid. There is consistent evidence that digital cervical examination is a weak predictor, and controversy regarding home uterine activity monitoring. There is scanty evidence about the predictive ability of maternal history and perceptions of symptoms since the study design fails to provide high evidence level. *Conclusion*: Cervical evaluation by vaginal sonography, fetal fibronectin and interleukin-6 are the best methods for predicting preterm birth.

1. Introduction

Preterm birth is defined as delivery before 37 weeks of gestation, and occurs in 8% to 11% of all pregnancies. This obstetric complication is responsible for 75% to 80% of all neonatal deaths [1—3], as well as a considerable infant and neonatal morbidity [4]. The etiology of preterm birth is related to the premature rupture of membranes in 30% of the cases, to maternal and fetal indications for early pregnancy termination in 20—25% and to spontaneous preterm births in about 40—45% of all cases [2,5].

Spontaneous premature birth has been associated with multifactorial causes, including demographic factors, stress, infections and genital inflammations. Bacterial vaginosis is also associated with spontaneous preterm birth [6]. It would be useful to have an effective method of predicting preterm birth so that early diagnosis could be made, and neonatal morbidity and mortality rates

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could be improved. Efforts are therefore being made to identify predictors of preterm birth, since some therapies, especially corticosteroids, are able to improve fetal prognosis [7].

The objective of this review is to identify the highest level of scientific evidence available in the literature with respect to possible predictors of preterm birth.

2. Method

This is a systematic review of published studies on possible predictors of preterm birth. Electronic databases (MedLine, Popline, SciELO and the Cochrane Library) were searched for published studies using the keywords: *preterm* and *birth* between January 1980 and August 2005. Initially, the citations were evaluated according to their titles and abstracts. When citations were considered of interest, their abstracts were obtained and assessed with respect to the quality of evidence provided, according to the criteria recommended by the US Preventive Services Task Force, as shown in Table 1 [8]. Whenever the information provided by the abstract was considered insufficient, the full article was retrieved for a more detailed analysis. The studies were grouped into the following categories: history; maternal perception of symptoms and signals; clinical examination; home uterine activity monitoring (HUAM); biochemical markers and imaging methods. For each category, the studies with the highest level of scientific evidence in predicting preterm birth were identified. These articles were retrieved, their method evaluated according to the level of scientific evidence [8] and their results and conclusions used to evaluate the level of scientific evidence available for each predictor.

Table 1 Grades of evidence and level of recommendations [8]

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Levels of recommendations	
A	The recommendations are based on good and consistent scientific evidence.
B	The recommendations are based on limited or inconsistent scientific evidence.
C	The recommendations are based primarily on consensus and expert opinion.

3. Results

A total of 8505 citations were identified from the electronic Internet search. After checking the information on study design, number of subjects, quality of the research methods and results, 59 complete studies were included in this review. Table 2 shows the highest level of evidence observed for each category and the conclusions regarding the performance of each predictor evaluated.

3.1. History

Socioeconomic status, clinical and obstetrical history, lifestyle, obstetrical examinations and other methods can be used to estimate the risk of preterm birth. A prospective analysis of the risk score system [9] is often mentioned in the literature to classify pregnancies as being of low-, medium- or high-risk for preterm birth, according to scores awarded for each parameter used.

In a large multicentric prospective analysis it was shown that the risk scoring system has low sensitivity (around 20%) and low positive predictive value (around 30%) for preterm birth [1]. Other prospective cohort study shows a linear relationship between food deprivation and preterm birth according to ethnic group and habits [10]. A low consumption of fish also seems to be a strong risk factor for preterm birth and low birth weight in Danish women [11].

Therefore, risk scoring systems fail to provide a satisfactory degree of evidence for predicting preterm birth because the types of study were unable to provide a high level of evidence. This is a weak predictor and there are various factors, such as dietary and local habits, that can bias the results.

3.2. Maternal perception of symptoms and signals

Pregnant women can be taught to recognize signals and symptoms of preterm labor. Uterine contrac-

Table 2 Highest level of evidence in predictors of preterm labor according to the classification of the US Preventive Services Task Force

Predictor	Level of evidence/recommendation	Conclusion/performance
History	II2-B	Weak evidence/unsatisfactory
Maternal perception of symptoms	II2-B	Weak evidence/unsatisfactory
Clinical exam	I-A	Good evidence/unsatisfactory
Home uterine activity monitoring	I-A	Good evidence/inconsistent
Interleukin-6	I-A	Excellent evidence/good
Fetal fibronectin	I-A	Excellent evidence/good
Vaginal ultrasound	I-A	Excellent evidence/good
Magnetic resonance imaging	II3-B	Poor evidence

tions are the most common symptom [12]. A case control study [13] showed sensitivity and specificity of 71% and 95%, respectively, for perception of contraction in an intervention group who received explanations on uterine contractions and preterm labor, compared to a control group who received no counseling. Moreover, a prospective study comparing self-palpation with uterine activity monitoring concluded that women were unable to perceive preterm uterine activity through self-palpation [14].

Reports from studies of high-risk populations have shown that symptoms have a low predictive value in women at risk of preterm birth [15]. Comparison of home uterine monitoring with symptoms and signs in a high-risk population showed that there was no significant difference in the predictive value of these methods [16].

The degree of evidence of maternal perception of contractions in low-risk populations is unsatisfactory; the studies have biases in the population and in the correct selection of women at risk for premature birth. There is insufficient evidence to recommend self-palpation as a predictor of preterm birth.

3.3. Clinical exam

Unfortunately, well-conducted studies with a good level of evidence have indicated poor efficacy of digital cervical evaluation and the Bishop score in predicting preterm birth. A study designed to evaluate the cervix by clinical examination and ultrasound in women at 28 weeks of gestation, considering a Bishop score >4 as cut-off point, resulted in sensitivity, specificity, positive and negative predictive values of 42.5%, 82.5%, 9.9% and 96.9%, respectively, for delivery prior to 35 weeks gestation [17].Studies with no significant bias and randomized controlled trials provide good evidence that clinical examination of the cervix has low predictive value in the prediction of preterm birth [18].

3.4. Home uterine activity monitoring (HUAM)

Home uterine activity monitoring (HUAM) is a system that needs trained nursing staff in order to detect preterm labor. Some randomized controlled trials have confirmed the beneficial effect of HUAM in high-risk pregnancies, increasing diagnosis of preterm labor [19,20] and improving performance of tocolytic agents [21,22]. In 1991, the US Food and Drug Administration approved this system for women who had had a previous preterm birth, thereby generating much controversy [23]. Some authors fail to see any advantage [24,25] and according to recommendations of the US Preventive Services Task Force [26], HUAM has not been indicated as a screening method for preterm labor and birth in high-risk pregnancies.

A multicentric randomized controlled trial [27] showed that HUAM failed to predict or reduce prematurity. On the other hand, other investigators have shown that IT succeeded in decreasing the risk of preterm birth, reduced the need for intensive neonatal care, and prolonged pregnancy [28—30]. A meta-analysis that evaluated six randomized trials on HUAM revealed significant benefits associated with reductions in risk of preterm birth in high-risk populations [28]. Dyson et al., comparing HUAM with different frequencies of contact with nurses, failed to find any favorable effect in either of the two study groups [31]. Another randomized trial studying HUAM following diagnosis of preterm labor showed that it failed to reduce the rate of birth before 35 weeks of gestation [32].

Although all these articles present a high degree of evidence, there is no consensus and the studies available were conducted only in high-risk populations. The most recent studies, however, fail to confirm it as a good predictor. There is strong evidence about the usefulness of HUAM, but the results are conflicting. A meta-analysis of recent studies is needed.

3.5. Laboratory methods

3.5.1. Interleukin-6 (Il-6)

Subclinical intra-amniotic infections possibly trigger preterm labor. Infection triggers cytokine production, as well as synthesis and release of prostaglandins, which are probably responsible for cervical ripening and uterine contraction.

There is a sufficiently high level of evidence in the literature to suggest that an increased level of interleukin-6 in the amniotic fluid is related to preterm birth. Nevertheless, a temporal relationship between increased Il-6 levels in the amniotic fluid and time of birth has yet to be established [33].

3.5.2. Fetal fibronectin

The presence of FNF in cervicovaginal secretions, amniotic fluid and placenta is normal until 21 weeks of pregnancy, but after that the fusion of membranes occurs and it is normally no longer released [34]. Based on this, the presence of FNF in vaginal or cervical secretions, detected by enzyme immunoassay between 21 and 37 weeks of gestation at levels >50 ng/ml, has been reported to be a predictor of preterm birth [35,36].

Women with symptoms of preterm labor were studied in a multicentric trial, showing that the presence of FNF in vaginal secretions defines a group with an increased risk of delivery within 7 days [37,38]. An overview concluded "...that the presence of fetal fibronectin in cervicovaginal mucus has limited accuracy in the prediction of preterm delivery..." [39], however, a meta-analysis conducted in patients with symptoms of preterm labor concluded that FNF is an effective predictor of preterm birth [40] and this information is in agreement with the results of another meta-analysis that confirms the presence of FNF in association with delivery before 34, 35 or 37 weeks gestation [41].

Systematic quantitative reviews claim that the cervicovaginal FNF is the most accurate in predicting spontaneous preterm birth within 7—10 days of testing among women with symptoms of preterm labor before cervical dilation [42,43]. There is a high evidence level proving that fetal fibronectin is a useful predictor for preterm birth and is able to estimate the preterm birth time.

3.6. Imaging methods

3.6.1. Transvaginal sonography

Transvaginal sonography has been used to evaluate the cervix as a predictor of preterm birth because it is more accurate than the digital examination [44,45]. Abdominal ultrasound for evaluation of the cervix has pitfalls that include the position of the cervix and the degree of bladder fullness, among others, but transvaginal sonography provides a good, clear view of the uterine cervix [46].

Several authors concluded that cervical length as measured by vaginal sonography was able to accurately predict preterm birth [17,47—51]. However, the cut-off point for cervical length is an important parameter to study and may vary in different study populations. Some authors have also reported this high-risk of preterm birth when the cervical length was less than 30 mm [49,50]. A systematic analysis suggests that cervical length ≤30 mm will identify 80% to 100% of those women who will have a preterm birth [46]. Recently the detection of the cervical gland area by endovaginal sonography has also been used as a predictor for preterm birth, but it real role is still to be determined [52]. A multicenter, observational study concluded that the only other factor associated with an increased risk of recurrent preterm birth was dilation [53].

Reports in the literature are in agreement that vaginal sonographic evaluation of cervical characteristics is a good method for predicting preterm birth, presenting an excellent level of evidence.

3.6.2. Magnetic resonance imaging (MRI)

Theoretically MRI is able to better assess the cervix, to diagnose cervical length, the signal intensity of cervical stroma, relaxation index, angles and diameters of the cervix and, moreover, is not operator-dependent [46,54]. It has been reported that during the last weeks of pregnancy there is an increase in tissue hydration in the cervix that can be measured by the signal intensity of the cervical stroma at MRI [55]. Although described in detail by some authors [54,56], no risk has yet been associated with MRI in human pregnancy [57]. Then, it is indicated for pregnant women when other imaging methods are inadequate or whenever it would provide important information that would otherwise require exposure to radiation [56].

At the moment there is insufficient evidence in favor of the use of MRI for the prediction of preterm birth and additional studies need to be carried out on this subject.

4. Discussion

A perfect predictor for preterm birth would be a test that had high accuracy, optimal sensitivity and specificity, and one that was readily available, affordable and precise [58]. Unfortunately, this

perfect method does not exist at the moment. The articles used in this review provide different levels of evidence and accuracy. Table 2 is a summary of the evidence level of preterm delivery predictors according to the classification used [8].

With respect to primiparous women, current knowledge on the risk score system suggests that this is an adequate method for distinguishing between low- and high-risk individuals; it is not, however, a good predictor and there may be a considerable bias involved [1,9]. Maternal perception of signals and symptoms is a poor predictor of preterm birth [14,15], the studies available failing to provide a good level of evidence. Moreover, these data may vary according to the population.

The most controversial method of prediction of preterm birth is Home Uterine Activity Monitoring since there have been no more than ten trials in the literature over the past ten years and the results of these studies are inconsistent [19—22,24,25,27, 30,32]. These differences between one study and another probably occur because they involve different populations at different times and with dissimilarities in interventions. Anyway, at the present time, this method is not recommended for predicting preterm birth in a low-risk population.

A cheap, easy and practical method of predicting preterm delivery may be the clinical cervical examination, but trials provide evidences that it has low predictive value for preterm birth. Laboratory methods, especially the measurement of fetal fibronectin, are very important predictors of preterm birth [39,40]. In patients with symptoms of preterm labor, the presence of fibronectin is related to delivery within 7 days [36,38]. Interleukin-6 is an already established predictor of preterm birth, furthermore, there is no known temporal relationship between interleukin-6 level and time until delivery [14].

Diagnostic imaging methods for the measurement of cervical length and for cervical evaluation are able to provide an accurate diagnosis [44,45]. Transvaginal sonography is a good predictor of preterm birth, however more studies need to be carried out in the general population, and its predictive value could be improved by complementing this examination with other markers [51]. Measurement of fetal fibronectin, together with evaluation of cervical length by transvaginal sonography may provide a satisfactory level of accuracy in the prediction of preterm birth [59,60].

According to the ACOG practice bulletin [61], screening for reasons other than historical risk factors is not beneficial to the general obstetric population. However, the use of ultrasonography for the evaluation of cervical characteristics, the assessment of fibronectin levels, or a combination of both, may be useful in diagnosing women at high-risk. The fetal fibronectin test alone may be useful in the case of women with symptoms of preterm labor.

5. Conclusion

There is strong scientific evidence that preterm birth may be predicted by using vaginal sonography to evaluate the cervix, by measuring fetal fibronectin in cervicovaginal secretions and interleukin-6 in the amniotic fluid. There is also consistent evidence that the digital cervical examination is a weak predictor and there is controversy with respect to home uterine activity monitoring. There is scanty evidence on the usefulness of maternal history or maternal perception of symptoms because the study designs fail to provide a high evidence level.

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