

Role of Progesterone for Maintenance Tocolytic Therapy: A Comprehensive and Updated Overview

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Preterm Labor

Preterm labor is defined as the occurrence of regular uterine contractions after the age of viability and before 37 completed weeks of gestation with intact membranes [1]. It is the leading cause of neonatal mortality and a substantial portion of all birth-related morbidity. Preterm delivery accounts for 65% of neonatal deaths and 50% of neurological disability in childhood. Prematurity rates have not changed in recent decades [2].

Threatened preterm labor:

is usually used to describe pregnancies complicated by episodes of clinically significant uterine activity but without cervical changes. Regular uterine contractions should be at least two every 10 minutes, while cervical changes refer to either dilatation or effacement (dilatation of 2 cm or more and cervical length of 1 cm or less) [3].

Preterm labour is multifactorial, it is associated with preterm rupture of membranes, cervical incompetence, polyhydramnios, fetal and uterine anomalies, infections, social factors, stress, smoking and heavy work [3].

Incidence:

The major burden of preterm birth is *in the developing world*, where most of the death and morbidity is secondary to infectious diseases such as malaria, Human Immunodeficiency Virus (HIV), tuberculosis, bacterial vaginosis and intestinal parasites [4].

The growth of the medical care industry in many developing countries had paradoxical effects on preterm birth, so that the highest rates of preterm birth are seen in the most affluent areas, associated with high caesarean section rates [5].

Barros et al. [6] have reported an eight-fold rise in caesarean section rates in Brazil over the past 20 years, associated with a three-fold rise in the incidence of preterm birth.

Preterm birth are rising *in many developed countries*, such as Denmark, probably due to the incidence of multiple pregnancy associated with assisted reproduction techniques as one in five preterm births is associated with multiple pregnancy [7].

In developed countries, more than one-third of preterm births are medically indicated, and delivery is by induction of labour or elective caesarean section [4].

Causes of preterm labor:

As the cause of labor still remains elusive, the exact cause of preterm birth is also unsolved. In fact, the cause of 50% of preterm births is never determined. Labor is a complex process involving many factors. Four different pathways have been identified that can result in preterm birth and have considerable evidence: precocious fetal endocrine activation, uterine over distension, decidual bleeding, and intrauterine inflammation/infection. Activation of one or more of these pathways may happen gradually over weeks, even months. From a practical point, a number of factors have been identified that are associated with preterm birth, however, an association does not establish causality [8]

Maternal background:

A number of factors have been identified that are linked to a higher risk of a preterm birth: age at the upper and lower end of the reproductive years, being more than 35 or less than 18 years of age [9]. Maternal height and weight can also play a role. Further, in the US and the UK, Afro-American and Afro-Caribbean women have preterm birth rates of 15–18%, more than double than that of the white population. This discrepancy is not seen in comparison to Asian or Hispanic immigrants and remains unexplained [9].

Pregnancy interval makes a difference as women with a 6 months span or less between pregnancies have a two-fold increase in preterm birth [10]. Studies on type of work and physical activity have given conflicting results, but it is opined that stressful conditions, hard labor, and long hours are probably linked to preterm birth [9].

Women who have undergone previous surgically induced abortions have been shown to have a higher risk of preterm birth (less than 37 weeks), as well as extreme preterm birth (less than 28 weeks) [11].

The preterm birth link has not been shown in women who terminated their pregnancies medically with pills such as mifepristone. Adequate maternal nutrition is important. Women with a low BMI are at increased risk for preterm birth [12].

Further, women with poor nutritional status may also be deficient in vitamins and minerals. Inadequate nutrition is critical for fetal development [10]. Obesity does not directly lead to preterm birth; however, it is associated with diabetes and hypertension which are risk factors by themselves. Women with a previous preterm birth are at higher risk for a recurrence at a rate of 15–50% depending on number of previous events and their timing [9].

To some degree those individuals may have underlying conditions (i.e. uterine malformation, hypertension, diabetes) that persist. Genetic make-up is a factor in the causality of preterm birth. An intra- and transgenerational increase in the risk of preterm delivery has been demonstrated. No single gene has been identified, and it appears with the complexity of the labor initiation, that numerous polymorphic genetic interactions are possible [13].

Prediction of Preterm Labor

Helpful clinical test should predict a high risk for preterm birth during the early and middle part of the third trimester, when their impact is significant. Many women experience false labor (not leading to cervical shortening and effacement) and are falsely labelled to be in preterm labor. The study of preterm birth has been hampered by the difficulty in distinguishing between "true" preterm labor and false labor. These new test are used to identify women at risk for preterm birth [8].

Predictors of preterm birth can be classified as *primary predictors*, predictors that are known before the onset of pregnancy and secondary predictors that may be present only after the onset of pregnancy [8].

Primary predictors:

Primary predictors include most of the classical risk factors for preterm birth (e.g. baseline characteristics, historical data, chronic maternal disease, lifestyle or socio- economic conditions). Primary predictors may be used to estimate the baseline risk of preterm birth and primary prevention would seek to modify these risk factors [8].

Secondary predictors:

Starting from the baseline risk, *secondary predictors* of preterm birth may help to adapt the risk of preterm birth during the course of pregnancy in individual women. Secondary markers would include signs, symptoms and findings in pregnancy that are would use these markers to provide interventions known to increase the risk of PTL. Secondary prevention would use these markers to provide interventions known to decrease the risk of preterm birth in selected high risk populations.

Primary prevention of preterm birth has been an important topic in public health for many years, whereas the screening for early signs has always been an important topic in practical obstetric care. Traditionally, attention has focused on symptoms suggestive of preterm labour and the results of the digital vaginal examination. During the last two decades, the detection of Fetal Fibronectin (FFN) from cervicovaginal secretions and cervical shortening diagnosed by transvaginal ultrasonography have emerged as the major secondary predictors of preterm birth [14].

History:

Women with a previous history of spontaneous PTB are 3.6 times more likely to deliver preterm spontaneously but 2.5 times more likely to have an iatrogenic PTB. Women who have had an iatrogenic PTB for medical indications are 10.6 times more likely to deliver preterm again for medical reasons and 1.6 times more likely to have a spontaneous PTB [15]. Women with a history of a previous PTB or a second trimester loss are at high risk of PTB [16]. Other factors that may be relevant are surgical termination of pregnancy, repeated dilatation and curettage [17].

Preterm labor index (tocolysis index):

In 1973, *Baumgarten and Gruber* proposed a tocolysis index for evaluating likelihood of preterm delivery, combining the four clinical factors of uterine contraction, Premature Rupture of Membranes (PROM), genital bleeding, and cervical dilatation. Because of premature rupture of membranes is a useful marker in itself; when it was present, 75% of patients already were in labor at admission, and another 10% delivered after spontaneous labor within 48% hours. So, a modified version of the tocolysis index, called the preterm labor index (excluding rupture of membranes) to evaluate the likelihood of preterm delivery in patients without PROM [18].

Preterm Labor Index (PLI) based on (uterine contraction, genital bleeding, and cervical dilation) and reported the likelihood of preterm delivery before 37 weeks and of delivery within 1 week in patients with a PLI score of 4 or higher as being 88.4% and 50.7%, respectively. This is significantly higher than the likelihood (55.2% and 10.3%) in patients with a PLI of 3 or lower [19].

Table (1): Preterm labor index

Sign	No. Points				
	0	1	2	3	4

Uterine Contraction (/h)	None	< 6	≥ 6
Genital bleeding (ml)	None	<10	≥ 10
Cervical dilation (cm)	None	1 to < 2	2 to < 3	3 to <4	≥ 4

Role of Progesterone in Preterm Labor

Women with a short cervix that received hormonal treatment with a progesterone gel had their risk of prematurely giving birth reduced. hormone treatment was administered vaginally every day during the second half of a pregnancy.

Women with a short cervix in the trial had benefit in two ways: a reduction in births less than 32 weeks and a reduction in both the frequency and the time their babies were in intensive care^[20]. Vaginal progesterone was shown to be better than placebo in reducing preterm birth prior to 34 weeks in women with an extremely short cervix^[21].

da Fonseca et al., (2013)^[22] suggested that vaginal progesterone could prevent preterm birth in women with a history of preterm birth. According to Harris (2011)^[23], women with a short cervix that received hormonal treatment with a progesterone gel had their risk of prematurely giving birth reduced. The hormone treatment was administered vaginally every day during the second half of a pregnancy.

Two new multisite randomized double-blind trials addressed the efficacy of progesterone in women at increased risk for preterm labor:

In the first study, 655 women with twin gestations received weekly intramuscular injections of 17P or placebo beginning at 16 to 20 weeks of gestation and ending at 35 weeks. Delivery or fetal death before 35 weeks was not significantly different in the two groups^[24].

In the second study, 413 women with cervical length of 15 mm or less on transvaginal sonography examination at 20 and 25 weeks of gestation received either vaginal progesterone or placebo from 24 to 34 weeks of gestation. Significantly, fewer women in the progesterone group than in the placebo group had a spontaneous birth before 34 weeks (19.2% versus 34.4%). However, no significant difference was observed in neonatal morbidity^[21].

Hassan et al., (2011)^[25] found that vaginal progesterone cut the risk of premature births by 42 percent in women with short cervixes. Sriram (2011)^[26] also found that the treatment cut the rate of breathing problems and reduced the need for placing a baby on a ventilator.

Progesterone in prevention of preterm labor is not known, although progesterone has been shown to prevent the formation of gap Junctions, to have an inhibitory effect on myometrial contractions, and to prevent spontaneous abortion. In women in early pregnancy after excision of the corpus luteum^[27].

Progesterone treatment reduced the number of uterine contractions and significantly reduced preterm delivery rates. This means that, while some women still delivered prematurely, progesterone treatment helped more- high risk women carry their pregnancies longer than a placebo treatment vaginal progesterone suppositories have been shown to decrease the rate of preterm birth in patients^[28].

The actions of progesterone on the pregnant myometrial muscle include relaxation of myometrial smooth muscle and block the action of oxytocin and inhibition of –the formation of the gap junctions^[27].

Progesterone also inhibits prostaglandine production by amnion –chorion, decidua and has been shown to increase the binding of progesterone in the fetal membranes at term (Mitchell, 1982).

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