Review Article

Preterm Labour - Prevention and Management: A Review

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Abstract:
In Bangladesh, among all live births, 22.3% were delivered prior to 37 weeks of gestation (preterm). Women with a history of spontaneous preterm delivery are 1.5 to 2 times more likely to have a subsequent preterm delivery. Preterm delivery (PTD) is the leading cause of neonatal morbidity and mortality, also one of the common reason for hospitalization during pregnancy. Preterm birth continues to provide an enormous challenge in the delivery of perinatal health care, and is associated with considerable short and long-term health consequences for surviving infants. Clinical diagnosis of preterm labor is made if there are regular contractions and concomitant cervical change. Less than 10% of women with a clinical diagnosis of preterm labor will deliver within seven days of initial presentation. Measuring cervical length and fetal fibronectin levels are two of the most accurate predictive tests for preterm birth, especially when use in combination. Other predictive tools like Actim Partus and Amnisure are effective for symptomatic women, but their role in surveillance of asymptomatic women is unclear. Cervical cerclage and use of progesterone is effective in reducing preterm birth in women with previous losses, but the role of pessaries remains debated. Steroids remain one of the most effective antenatal intervention, but they need to be administered within a tight time frame in order to confer maximal benefit. A course of corticosteroids is the only antenatal intervention that has been shown to improve post-delivery neonatal outcomes, including a reduction in neonatal mortality, intracranial hemorrhage, necrotizing enterocolitis, and neonatal infection. Tocolytics, especially prostaglandin inhibitors and calcium channel blockers, may allow time for the administration of antenatal corticosteroids and transfer to a tertiary care facility if necessary. When used in specific at-risk populations, magnesium sulfate provides neuro protection and decreases the incidence of cerebral palsy in preterm infants.

Keywords: progesterone, preterm labor, tocolytics

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Introduction:
Preterm birth, is defined by the World Health Organization as birth prior to 37 completed weeks of gestation[1]. It is multifactorial in origin, with approximately two-thirds of all preterm births occurring spontaneously, but the other third there is maternal or fetal indication for early delivery[2].

Fifteen million preterm births occur every year and this number is rising. One million babies die from preterm birth complications annually. Five to eighteen percent is the range of preterm birth rates across 184 countries of the world; >80% of preterm births occur between 32-37 weeks of gestation, and most of these babies can survive with essential newborn care[3]. In Bangladesh, among all live births, 22.3% were delivered prior to 37 weeks of gestation (i.e. preterm); of which 12.3% were born at 35–36 weeks of gestation (late preterm), 7.1% were born at 32–34 weeks (moderate preterm), and 2.9% were born at 28–31 weeks of gestation (very preterm)[4]. Preterm neonates are at higher risk of complications, including respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, and sepsis. They are also at significantly increased risk of developing cerebral palsy, visual impairment, and intellectual disability. As adults, children born preterm and at low birth weights are at increased risk for chronic lung disease, cardiovascular disease, and diabetes mellitus[5].

Given the effect of preterm birth on neonatal morbidity and mortality, there has been much effort dedicated to the investigation of prevention strategies. Unfortunately, interventions, such as tocolytics, antibiotics and home uterine monitoring, have all been found to be of minimal benefit, no benefit or potentially harmful. However, treatment with progesterone has emerged as a potentially effective intervention for the prevention of preterm birth in high-risk populations[6].

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The aim of this review article, to focus the predictive tests (cervical length, fetal fibronectin, Actim Partus, Amnisure) and prophylactic interventions (cerclage, progesterone, Arabin pessary, antibiotics, and steroids) and the role of some drugs (magnesium sulfate and tocolytics) for preterm birth and how effective they are.

Predicting Pre Term Labour (PTL)

Cervical Length:

The cervix physiologically changes and shortens during normal labour, however these changes are highly predictive of PTL if they occur <32 weeks spontaneously or after inflammation, haemorrhage, premature contractions, or uterine over distension[7]. A short cervix identified by ultrasound is associated with increased risk of PTL <35 weeks in symptomatic and asymptomatic women with singleton and twin pregnancies. Trans vaginal ultrasound scans (TVUSS) are accurate, safe, well accepted, reliable, valid in low and high risk women, and a systematic review concluded that cervical length (CL) < 25mm between 16-24 weeks is the most reliable marker for PTL[8].

Nitrazine test:

A positive Nitrazine test result (pH of 7.1 to 7.3), arborization or ferning on microscopy, and pooling of fluid in the vaginal vault during speculum examination are indicators of ruptured membranes.

Amnisure:

Tests for amniotic proteins, such as placental alpha microglobulin-1 (Amnisure), have high reported sensitivity for premature rupture of membranes[9]. Most women presenting with preterm premature rupture of membranes will deliver within one week[10].

Recent Upgrade for Evaluation of PTL

Fetal fibronectin (fFN) testing:

When further evaluation is necessary to predict preterm delivery, fetal fibronectin test can be done. Fetal fibronectin (fFN) is a glycoprotein produced by amniocytes and cytotrophoblasts. It appears in cervical secretions before the onset of labour. The fetal fibronectin test has a high negative predictive value. A patient who tests negative has a low probability of delivery within the next 14 days[11].

Actim Partus:

The test is qualitatively measures CVF levels of phIGFBP-1 (phosphorylated insulin-like growth factor binding protein). Similarly to fFN, the protein levels increase following placental-decidual disruption and can be detected before labour[12]. phIGFBP-1 level are as good as predicting delivery <35 weeks in women having contractions as fFN, but are not affected by urine contamination or sexual intercourse within the previous 48 hours, which gives it an advantage over fFN.

Risk Factors for Preterm Delivery

Unmodifiable risk factors include a shortened cervix (less than 25 mm before 28 weeks gestation) and a history of preterm delivery[13].

Women with a prior preterm delivery have a 1.5 to two fold increased risk of a subsequent preterm delivery[14]. A history of cervical conization or a loop electrosurgical excision procedure of the cervical transformation zone also increases the risk of preterm delivery.

Infections of the urinary and genital tracts and periodontal disease have been associated with an increase in preterm delivery[15].

Behavioral risk factors include low maternal pre pregnancy body mass index (19.8 kg per m2 or less), maternal smoking, substance abuse, and a short pregnancy interval (less than 18 months between pregnancies)[16].

High fish consumption has been linked to a decreased incidence of preterm delivery, but taking omega-3 fatty acid supplements has not been shown to be beneficial[17].

Mechanism of Preterm Birth

The precise hormonal and molecular mechanisms underlying preterm birth remain under investigation. Available evidence suggests that a complex cascade of hormonal and inflammatory events leads to an increase in uterine activity, onset of cervical remodeling, and membrane activation (Figure 1)[18].

Prevention of Preterm Labour (PTL)

Progesterone Therapy:

Progesterone is a steroid hormone secreted by the corpus luteum and by the placenta after 8 weeks of gestation. In women with single gestation pregnancy and a history of spontaneous preterm delivery, antenatal progesterone therapy is the most effective strategy to decrease the risk of a recurrent preterm delivery. Progesterone supplementation is beneficial in these women starting at 16 to 24 weeks of gestation and continuing through 34 weeks of gestation[19].

In a randomized placebo-controlled trial, treatment with vaginal micronized progesterone, 200 mcg daily, was associated with a 44% reduction in spontaneous preterm delivery in asymptomatic women with a cervical length of 15 mm or less at 20 to 25 weeks of gestation[20]. Progesterone is not beneficial in multiple gestation pregnancies.

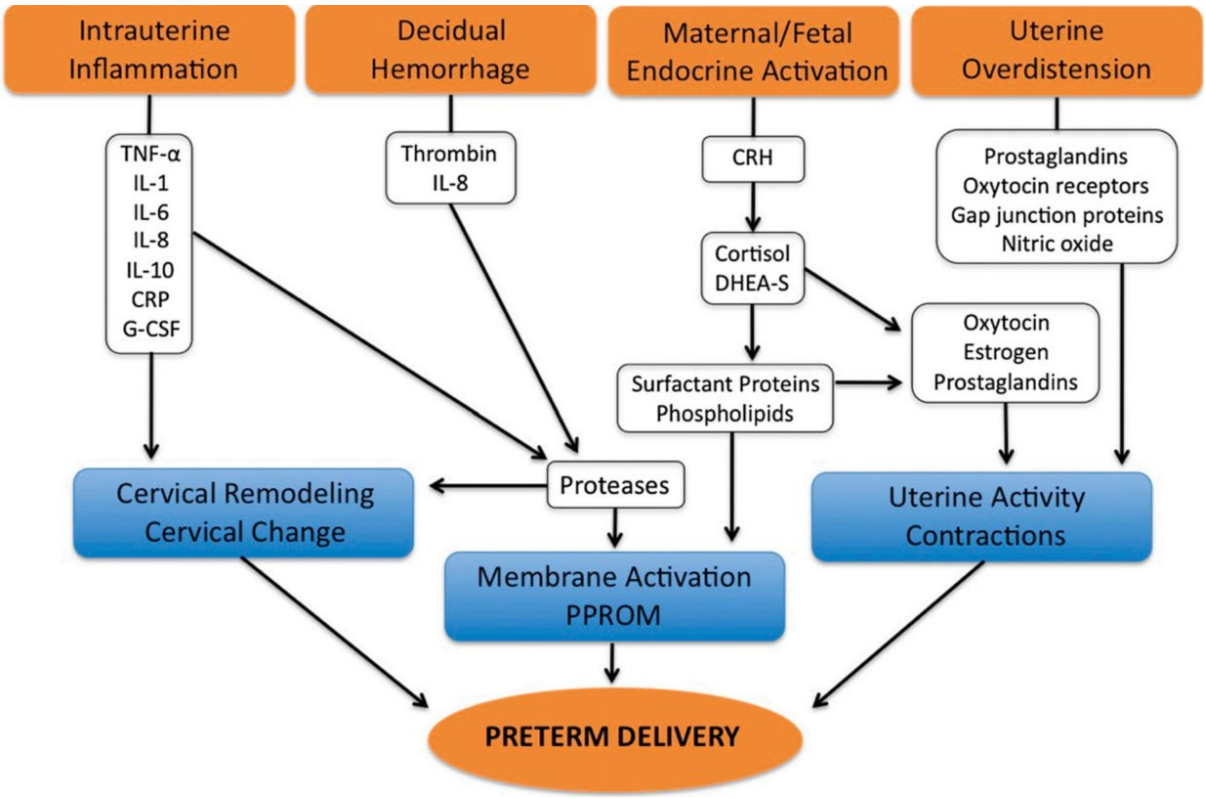

Figure-1: The preterm birth pathway consists of complex and poorly understood hormonal and molecular interactions[18]. CRH=corticotropin releasing hormone; CRP=C-reactive protein; DHEA S=dehydroepiandrosterone sulfate; G-CSF=granulocyte colony stimulating factor; IL=interleukin; PPROM=preterm premature rupture of membranes; TNF=tumor necrosis factor.

Table-I: Current Indications for Progesterone Use in Pregnant Women

Indication	Treatment regimes
1. History of preterm delivery <37 weeks gestation	1. 17-OHP, 250 mg IM given once weekly, from 16 to 36 weeks gestation
2. Asymptomatic shortened cervix (TVCL <20 mm) diagnosed at <25 weeks gestation	2. Per Vaginal progesterone given nightly until 34-37 weeks gestation

Progesterone has a role in maintaining pregnancy, by suppression of the calcium–calmodulin–myosin light chain kinase system. Additionally, progesterone has recognized anti-inflammatory properties, raising a possible link between inflammatory processes, alterations in progesterone receptor expression and the onset of preterm labor[18].

Systematic reviews of randomized controlled trials evaluating the use of intramuscular and vaginal progesterone in women considered to be at increased risk of preterm birth have been published[19]. Current recommendations are to prescribe vaginal progesterone in women with a shortened cervix and no history of preterm delivery, and to use progesterone supplementation regardless of cervical length in women with a history of spontaneous preterm delivery[20].

Cervical cerclage:
Cervical cerclage, an encircling suture placed around the cervix before or during pregnancy, has been used to help correct structural defects or cervical weakening in high-risk women with a shortened cervix. Studies have shown that cerclage is associated with a decrease in preterm delivery and in perinatal death when used in women with a prior preterm delivery and a cervical length of 25 mm or less[21].

Cervical Pessary
Arabin Pessary: The Arabin pessary is a flexible silicone ring that is inserted into the vagina to prevent PTB in women with short cervixes[22]. The mechanisms of action are debated, but it may be through mechanical support of the uterus, changing the utero-cervical angle or by strengthening the cervical mucus plug, which is protective against infection. With further studies, the cervical pessary may be promising noninvasive additional

intervention to prevent preterm delivery in women with a shortened cervix[23].

Management of Preterm Labour:

Corticosteroid therapy:

Once preterm labour is confirmed, a single course of corticosteroids is the only intervention for improving neonatal outcomes. Betamethasone, two 12-mg doses given intramuscularly 24 hours apart, or dexamethasone, four 6-mg doses given intramuscularly every 12 hours, is recommended between 24 and 34 weeks gestation, and may be considered as early as 23 weeks gestation, in women likely to deliver within seven days regardless of membrane status[24].

Magnesium sulfate:

Because of its neuroprotective effect, administration of antenatal magnesium sulfate has been associated with a decrease in occurrence and severity of cerebral palsy in infants[25]. The side effects of magnesium sulfate are maternal respiratory depression, diplopia, muscle paralysis and rarely cardiac arrest.

Tocolysis:

Many studies have shown that tocolytic agents are effective for 2-7 days, a golden time to administer corticosteroids to mature the fetal lungs. Tocolytic agents are contraindicated in placenta abruption, intrauterine infection, fetal anomalies and placenta previa[26].

*Medication**	*Dosage*	*Maternal adverse effects*
Nifedipine (calcium channel blockers)	30-mg loading dose orally, then 10 to 20 mg every 4 to 6 hours (maximal dosage: 180 mg per day)	Dizziness, flushing, and hypotension; suppressio of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate; elevation of hepatic transaminase level
Indomethacin (prostaglandin inhibitor, nonsteroidal anti-inflammatory drug)	50- to 100-mg loading dose orally or rectally, then 25 to 50 mg orally every 4 to 6 hours; therapy is not recommended for greater than 48 hours because of potential change in amniotic fluid levels and premature closing of fetal ductus arteriosus	Nausea, esophageal reflux, gastritis, emesis; platelet dysfunction is rarely of clinical significance in patients without an underlying bleeding disorder
Terbutaline (beta-adrenergic receptor agonist)	0.25 mg subcutaneously every 20 to 30 minutes for up to four doses or until tocolysis is achieved, then 0.25 mg every 3 to 4 hours until the uterus is quiet for 24 hours Alternate dosage: 2.5 to 5 mcg per minute via intravenous infusion, increasing by 2.5 to 5 mcg per minute every 20 to 30 minutes to a maximum of 25 mcg per minute or until the contractions have abated; at this point, the infusion is reduced by decrements of 2.5 to 5 mcg per minute to the lowest dose that maintains uterine quiescence Therapy should not be continued longer than 48 to 72 hours because of serious adverse effects	Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia
Magnesium sulfate	6-g bolus intravenously over 20 minutes, then 2 g per hour as continuous infusion	Flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, and cardiac arrest; suppression of heart rate, contractility, and left ventricular systolic pressure; produces neuromuscular blockade when used with calcium channel blockers

*—Listed in order of preference.

Figure-2: Tocolytics recommended for the management of preterm labour[27]

Antibiotics:

Intrauterine bacterial infections are associated with preterm labour, especially before 32 weeks gestation. Although several trials have been conducted, no studies have shown that use of antibiotics during preterm labour is effective in delaying delivery or reducing neonatal morbidity associated with preterm delivery[28].

Discussion:

In this review article we deliberately explain the various aspects of diagnosis, mechanism, management and prevention of pre-term delivery. There are many studies and surveys were made in this regard[26,27,28]. Studies from distant countries shows us the various aspects of method we can use to minimize the incidence of this condition[27,28]. There are some copious numbers of methods we discussed here for the management and prevention of this condition like using recent advance diagnostic system in case of prediction and applying tocolytics and progesterone for the avoidance of its occurrence[26].

A recollected study shows us utilization of recent advance diagnostic systems like combination of

measuring fetal fibronectin and trans-vaginal ultrasound for measuring of cervical length are beneficial for diagnosis of this condition[29]. And can also use methods like Amnisure and Actim partus for this purpose.

For management purpose we can get benefit from practicing various options including corticosteroid therapy, magnesium sulfate, tocolytics and using of antibiotics[30]. Application of tocolytics has a huge role in the management of this condition[31]. This drug have not been shown to reduce the number of the pre-term deliveries but can prolong the pregnancy[32]. Among the tocolytics which have been previously mentioned the calcium channel blockers, β-adrenergic receptor agonists, Non-steroidal Anti Inflammatory drugs has the great beneficial effect[33].

For the intention of prevention of this condition we greatly use the progesterone. There are two options available in this regard like application of injectable form of progesterone that is 17-OHP and other is vaginal progesterone[33]. Vaginal progesterone also plays a role in suppression of premature labour related to magnesium sulfate and also different studies have not shown any adverse effect related to progesterone[34].

Conclusion:

Preterm birth is a major cause of neonatal morbidity and mortality worldwide. The pathogenic pathways that lead to preterm birth are multiple and complex. Significant research efforts continue to be dedicated to understanding the preterm birth pathways in an effort to improve existing and develop new preventive interventions.

References:

1. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977; 56 (3): 247-53.

2. Moutquin JM. Classification and heterogeneity of preterm birth. BJOG. 2003; 110 (Suppl 20): 30-3.

3. Blencowe H, Cousens S, Oestergaard MZ, *et al*. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379 (9832): 2162-72.

4. Shah R, Mullany LC, Darmstadt GL, *et al*. Incidence and risk factors of preterm birth in a rural Bangladeshi cohort. BMC Pediatr. 2014; 14: 112.

5. Brehaut JC, Kohen DE, Garner RE, *et al*. Health among caregivers of children with health problems: findings from a Canadian population based study. Am J Public Health. 2009; 99 (7): 1254-62.

6. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. Obstet Gynecol. 2007; 110 (2 pt 1): 405-15.

7. Ross MGN, Ridout AE, Shennan AH. Promising recent advances in pre term birth management. Front womens healt. 2016; 1 (2): 27-33.

8. Grimes-Dennis J, Berghella V. Cervical length and prediction of preterm delivery. Curr Opin Obstet Gynecol. 2007; 19 (2): 191-5.

9. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins - Obstetrics. Practice bulletin no. 172: Premature rupture of membranes. Obstet Gynecol. 2016; 128 (4): e165-77.

10. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm delivery. Lancet. 2008; 371 (9606): 75-84.

11. Dodd JM1, Flenady VJ, Cincotta R, *et al*. Progesterone for the prevention of preterm birth: a systematic review. Obstet Gynecol. 2008; 112 (1): 127-34.

12. Khambay H, Bolt LA, Chandiramani M, *et al*. The Actim Partus test to predict pre-term birth in asymptomatic high-risk women. J Obstet Gynaecol. 2012; 32 (2): 132-4.

13. Iams JD, Goldenberg RL, Meis PJ, *et al*. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med. 1996; 334 (9): 567-72.

14. Hassan SS, Romero R, Vidyadhari D, *et al*. Vaginal progesterone reduces the rate of preterm delivery in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2011; 38 (1): 18-31.

15. Newham JP, Newham IA, Ball CM, *et al*. Treatment of periodontal disease during

pregnancy: a randomized controlled trial. Obstet Gynecol. 2009; 114 (6): 1239-48.

16. Hickey CA, Cliver SP, McNeal SF, Goldenberg RL. Low pregravid body mass index as a risk factor for preterm delivery: variation by ethnic group. Obstet Gynecol. 1997; 89 (2): 206-12.

17. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. Am J Obstet Gynecol. 2005; 193 (4): 1292-301.

18. Salati J, Caughey AB. Progesterone for the prevention of preterm birth. NeoReviews. 2014; 15 (11): e484-92.

19. Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol. 1990; 97 (2): 149-54.

20. Fonseca EB, Celik E, Parra M, *et al*. Progesterone and the risk of preterm delivery among women with a short cervix. N Engl J Med. 2007; 357 (5): 462-9.

21. Owen J, Hankins G, Iams JD, *et al*. Multicenter randomized trial of cerclage for preterm delivery prevention in high-risk women with shortened mid trimester cervical length. Am J Obstet Gynecol. 2009; 201 (4): 375. e1-8.

22. Arabin B, Alfirevic Z. Cervical pessaries for prevention of spontaneous preterm birth: past, present and future. Ultrasound Obstet Gynecol. 2013; 42 (4): 390-9.

23. Committee on Practice Bulletins - Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012; 120 (4): 964-73.

24. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2017, Issue 3. Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004454.pub3/epdf/abstrac [Accessed on July 25, 2018]

25. Marret S, Marpeau L, Zupan-Simunek V, *et al*. Magnesium sulphate given before very-preterm delivery to protect infant brain: the randomised controlled PREMAG trial. BJOG. 2007; 114 (3): 310-8.

26. Resnik R. Issues in the Management of Preterm Labor. J Obstet Gynaecol Res. 2005; 31 (5): 354-8.

27. Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. Obstet Gynecol. 2009; 113 (3): 585-94.

28. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins Obstetrics. Practice bulletin no. 171. Management of preterm labor. Obstet Gynecol. 2016; 128 (4): e155-64.

29. Iams JD. Prediction and early detection of preterm labor. Obstet Gynecol. 2003; 101 (2): 402-12.

30. Sayres WG Jr. Preterm labor. Am Fam Physician. 2010; 81 (4): 477-84.

31. Peaceman AM, Andrews WW, Thorp JM, *et al*. Fetal fibronectin as a predictor of preterm delivery in patients with symptoms: a multicenter trial. Am J Obstet Gynecol. 1997; 177 (1): 13-8.

32. Lefebvre F, Glorieux J, St-Laurent-Gagnon T. Neonatal survival and disability rate at age 18 months for infants born between 23 and 28 weeks of gestation. Am J Obstet Gynecol. 1996; 174 (3): 833-8.

33. Chow SSW, Marsney RL, Hossain S, Haslam R, Lui K. Report of the Australian and New Zealand Neonatal Network, 2013. Available at: https://npesu.unsw.edu.au/sites/default/files/npesu/data_collection/Report_of_the_Australian_and_NewZealand_Neonatal_Network_2013.pdf [Accessed on July 25, 2018]

34. Coomarasamy A, Thangaratinam S, Gee H, Khan KS. Progestrone for The Prevention of Preterm Birth: A Critical Evaluation of Evidence. Eur J Obstet Gynecol Reprod Biol. 2006; 129 (2): 111-8.

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