# Actual options in prevention of premature labor

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***Contents***

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## *Summary:*

The aim of this thesis is to review the current options for treating premature labor. It will focus on evaluating the efficacy of the various therapies based on the comparisons of data presented in available articles on clinical trials. The results show that many of the treatments used today yield little or no improvement. And for those that are proven to be effective it is difficult to distinguish the patients that can benefit from the treatment from those that will not.


## Introduction:

Premature labor is defined as birth before 37 weeks of gestation. It is a major health problem all around the world because of the increased neonatal morbidity and mortality, long-term sequella in this group of patient and the economic costs to society. Statistics show an increase in the rate of preterm birth around the world. This is partly thought be due to the increased use of IVF, the increase in the number of multiple births, higher age of mothers and possibly changes in the definition of preterm labor.

An analysis of the birth rates recorded for 2005 by WHO showed that around 9,6% of all birth in the world were preterm. The numbers varied geographically with the lowest incidence found in Europe (6,2%) and the highest found in Africa and North America (11,9% and 10,6%). [Beck 2010]

A distinction is usually made between preterm births that occur spontaneously and those that are induce to benefit the health of the mother or the child. Around 45-50% of preterm births are idiopathic, 30% follow premature rupture of membranes and 15-20% are induced due to medical indications [Beck. 2010]

The etiology of preterm birth is unknown, but it is thought to be multifactorial. There is probably not only one process, but rather several different processes with different triggers that lead to the same result, namely changes in the myometrium and cervix that result in the birth. Acknowledged risk factors for spontaneous preterm birth are smoking, low maternal BMI, decreased cervical length, black race and previous preterm delivery.

Attempts are being made at finding methods of screening pregnant women to detect those that are at increased risk of preterm labor and also to identify the women who are most likely to benefit from the different options of treatment.

The risk factors mentioned above identify some of the women, The most important of them are the women who have a history of preterm birth. With each child born prematurely, the risk of the next pregnancy ending before term increases. Regular transvaginal ultrasound controls will help identify the women with shortened cervix (less than 25 mm at 20-24 weeks). Fetal fibronectin is normally found between the fetal membranes and the uterine wall. When it is found in vaginal secretions before birth this can be an indication that the woman is at risk for preterm birth. Trials show that it as a marker of preterm birth fetal fibronectin has relatively high specificity, but low sensitivity. [Spong 2007].

## *Review of the current knowledge of options for treating premature labour*

### Cervical cerclage

In some pregnancies the normal processes that lead to birth begin too early. If there are signs of painless cervical shortening and dilation of the cervix before week 24 it is a sign of cervical insufficiency. The condition is difficult to diagnose because the diagnostic criteria are not clear and the pathogenesis is not well understood.

A widely used treatment option for these patients is the placement of a cervical cerclage.

The procedure involves the placement of stitches in the cervix to hold it closed in an attempt to prevent premature delivery. The stitches are removed when the pregnancy is close to term.

The time of placement of the cerclage varies according to the indication. If the patient has a history of preterm delivery, or belongs to the group of patients at high risk the cerclage is placed early – typically between weeks 12 and 15. If there are sign of cervical insufficiency the cerclage is placed when the patient presents with these signs.

Cervical cerclage is performed in patients with a relatively wide variety of indications, but the three main types of cerclages are described here according to the indication.

### History-indicated cerclage:

Women with a history of second trimester loss or preterm delivery may be given an elective cerclage. This is usually done around 14-24 weeks when most of the unavoidable miscarriages will already have taken place.

Most of the patients that have been treated since the procedure was first described by Shirodker in 1955 have belonged to this group of patients. Despite this there are surprisingly few clinical studies, most of which are several decades old and are not proper "controlled" studies. [Fox 2010]

There have only been five randomized clinical trials published so far. They were described in articles by Fox et a.l and Daskalis et al. and a summary of the results is given here. [Fox 2007, Daskalis 2009]

Dor et al. performed a randomized trial in 1982 consisting of 50 women expecting twins. The results showed that there was no difference in the outcome of the women who had had the operation and those that did not.

Lazar et al. performed a randomized study in 1984 on 506 women with pregnancies that were considered low-risk for preterm delivery and found that there was no change in length of gestation or neonatal survival for the women who had a cerclage and those that received expectant management

The same year Rush et al. reported on 194 women with high-risk pregnancies. Women that were smokers, older than 35 years, pregnant with twins or that had any preexisting pathologic condition of the uterus were excluded from the trial. Also in this trial there were found no difference in the outcome.

The largest randomized trial on history–indicated cerclage was performed in 1993 by the Medical Research Council of the Royal College of Obstetricians and gynaecologists. The 1292 women selected had histories that were not typical for women with cervical insufficiency and where the treating doctor was uncertain as to whether the patient should be given a cerclage. The results showed that the cerclage group had lower incidence of preterm birth than the control group – 13% versus 17%. The only subgroup of the women where the reduction was significant was women with three or more second trimester losses or preterm deliveries.[Fox 2007]

The most recent study was done by Althuisius et al in 2003. It was a study in two parts. In the first part 67 women with a history indicative of cervical insufficiency were either given a cerclage or serial ultrasonographic cervical assessment. There was no significant difference.

It is worth noting that none of the trials were specific for women with cervical insufficiency which is what the cerclage is meant to oppose.

## Ultrasound-indicated cerclage

Shortening of the cervix is a risk factor for preterm birth. It can be detected earlier by using ultrasound than by physical examination. The shortening is a risk factor for preterm birth. There have been conducted four randomized trials with the aim to find out if cerclage is a treatment that works for these patients.

Rust et al. performed study with 113 women who had ultrasound finding showing cervical length of less than 25 mm or 25% funneling. All women had an amniocentesis and were given antibiotics to rule out infection. The results showed no significant difference between the women given a cerclage and the women who were not.[Daskalakis 2009]

The second part of the trial performed by Althiusius et al. described above was on women with a history that put them in the high-risk group. There were done regular ultrasound scans of the women and those that had a shortening of the cervix were either given a cerclage or assigned to bed rest. On analysis there was found a statistical significant decrease in premature delivery (0 vs. 43%). [Fox 2007]

To et al.  performed a study where 253 women with cervical lengths found to be less than 15 mm were either given a cerclage or no treatment. There was no difference of the result between the two groups. Bergerhella et al. performed a trial on 61 patients with cervical length less than 25 mm and obtained the same results- no difference.

A meta-analysis performed by the four authors mentioned above showed that with this increased sample size there was an overall 17% reduction of preterm births in patients who received an ultrasound-indicated cerclage. The most significant reduction was in women with a history of premature delivery or a second-trimester loss.

A study done by Sakai in 2006 which provided data that showed that women with negative test for IL8 in cervical mucus there was a reduction in preterm delivery. This indicates that some of the women who did not benefit from the cerclage may have had a subclinilcal infection which affected the outcome. [Fox 2007, Daskalakis 2009]

### Physical examination-indicated cerclage

Women who present with dilation of the cervix and bulging of membranes on examination in the second trimester are considered to be at very high risk for imminent preterm delivery. Very few studies have been conducted that evaluate the effect of cerclage in these patients.

There has been only one randomized trial to evaluate physical examination-indicated cerclage. It was performed by Althuisius et al. in 2003. 23 women with bulging of the membranes prior to $27^{th}$ week were arranged randomly into two groups. One group received an emergency cerclage and indomethacine, the other group received no treatment. The results showed that the women who received a cerclage had an increase in length in duration of pregnancy, but the neonatal survival rate was the same. However the sample is too small for the results to be conclusive. [Fox 2007]

Fox and Chervenak deskrives two other studies in their review article. These results were not randomized, but the results support the findings of Althiusius' study.

## Progesterone

Progesterone has several functions that may suggest that it has a positive effect in reducing preterm birth. It reduces contractility of uterine smooth muscle by decreasing conduction of contractions and increasing the threshold for stimulating contractions. It also reduces the expression of oxytocin receptors. However, the actual method of action in prevention of birth is incompletely understood. [Spong 2007].

Numerous studies have been conducted on the effect of progesterones versus placebo in reducing preterm birth with varying results. Da Fonseca et al. performed a randomized trial with 142 at risk women that were either given progesterone or a placebo. The results showed a significant decrease in preterm birth before 34$^{th}$ week [Spong 2007]. Meis et al. randomized 463 women with a history of spontaneous preterm birth. They were either given 17α hydroxyprogesterone caproate or placebo. This trial also showed a significant decrease in birth before 37th, 35$^{th}$ and 32$^{nd}$ week, in addition it also showed a decrease in neonatal morbidity, respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis [Spong 2007].

Two recent meta-analysis Dodd et al. and Sanchez-Ramos et al. evaluated the benefits of progesterone treatment for prevention of preterm birth and for neonatal outcome [Dodd 2007, Sanchez-Ramos 2005]. The analysis included 11 and 10 randomized studies – 8 were the same. (Da Fonsecas and Meis' studies were among these). The quality of all the trials was assessed and those found lacking because of incorrect method or indications of treatment were excluded from the analysis. The analysis by Dodd et al. the studies were subdivided according to the patients' symptoms and the results were evaluated accordingly. The conclusions reached for the two analyses differ. According to Sanchez-Ramos the results showed a decrease in preterm birth for patients at increased risk. There was also noted a decrease in perinatal mortality, but this was not statistically significant and he concluded that further investigation is needed. Dodd et al. found that progesterone has a beneficial effect in reducing preterm birth for some women [Dodd 2008]. They went on to look at the results for the different subgroups. There was a significant reduction for women with a history of preterm delivery. There was also a decrease for women for whom the indication had been ultrasound detection of shortened cervix. No difference was found for perinatal death between the placebo and the progesterone groups. The same was the case for multiple pregnancies –

however there was only one trial assessing this. The dose and method of administration for progesterone were also considered, but the results were not conclusive.

## Tocolytics

Tocolytics are drugs given to women in an attempt to stop preterm birth when contractions have begun. The drugs that have an effect delay delivery by 48 hours or more and its main importance in in allowing the administration of steroids.

It is important to determine at what gestational age tocolytics has the greatest effect. If the assumption is that the main importance of the therapy is the possibility to give corticosteroids it would appear logical that the earlier tocolytics is given after the $24^{th}$ week, the greater the effect. A decision analysis by Macones et al. concluded that at 32 weeks treatment with tocolytics was preferred over no treatment. At 34 weeks the outcomes were the same and at 36 weeks no tocolysis was to be preferred [Macones ].1998

### Beta mimetics

The beta-adrenergic-receptor agonists ais a much studied group of tocolytic drugs. They work by binding to $\beta_2$ adrenergic receptors in myometrial cells. The binding leads to an increase in cyclic AMP level which in turn leads to inactivation of myosin light chain kinase and myometrial relaxation. Ritodrine is the beta-mimetic agent that is used most frequently. [Blumfeld 2009]

Meta-analysis of beta mimetics show a delay in birth compared to placebo. [Simhan 2007], Despite of these findings they are not among the first choices in preventing preterm labour due to the side effect for the mother. Common side effects include tachycardia, hyperglycemia, nausea, dyspnea and tachyphylaxis. No significant reduction in perinatal mortality or morbidity has been detected with the use of beta mimetics. [Simhan 2007]

## Magnesium sulfate

Magnesium sulfate is the tocolytic agent most commonly used in the United States [Blumfeld 2009]. The mechanism of action is by competing with intracellular calcium and inhibiting myosin light-chain kinase. Extracellular magnesium inhibits calcium channels, decreasing calcium influx and thereby reducing uterine contractility.

The majority of women experience side effect like nausea, vomithing, lethargy, dizziness and headache from taking it. In some patients there are more serious side effects like chest pain, dyspnea and cardiac arrest.

Studies show contradictory results as to the effect on the neonate. Some report increase in the length of stay in the intensive care unit compared to neonates whose mothers had received another tocolytic . Others propose a neuroprotective effect as some studies have shown a decrease in cerebral palcy in children of mothers who received magnesium sulfate. [Blumfeld 2009],

Mercer and Merlino performed a meta-analysis based on 19 randomized trials evaluating the effect of magnesium sulfate versus other tocolytics [Mercer BM]. The results showed no effect in preventing preterm birth nor did it affect the neonatal outcome and the authors recommendation was that it should not be used to treat women at risk of preterm delivery. The analysis did however support the findings that it has a neuroprotective effect if given prophylactically.

## Calcium channel blockers

These drugs work by blocking calcium channels, decreasing the concentration of intracellular calcium and in that way decreasing the force of contraction of the myometrium. Nifedipine is the calcium channel blocker that has been studies the most [Blumfeld 2009]. There are

however no studies where the control group received placebo, instead all studies involving nefedipine compared its efficacy in delaying birth to that of other tocolytic agent. A meta-analysis performed by King et al, involved 12 randomized trials comparing the effect of nifedipin to that of beta-mimetics and other tocolytics. The results showed that nifedipine therapy yielded the best improvement in outcomes. There was also noted a reduction in neonatal morbidity, and less maternal side effects than with beta-mimetics. [Simhan H],

### Cyclooxygenase inhibitors

These drugs prevent the conversion of arachidonic acid to prostaglandins. Prostaglandins influence the intracellular calcium by increasing the gap junctions in the myometrium. There are two isoforms of cyclooxygenase. COX-1 is constantly present in the decidua and in the myometrium whilst the expression of COX-2 increases considerably during term and preterm labor.

The COX inhibitor most commonly used is indomethacin [Blumfeld 2009], It is nonselective for the isoforms of the enzyme. A COX-2 inhibitor that has been subject for some trials is nimesulide, however as of yet there is not enough evidence to advocate its use. [Simhan 2007]

Randomized trials have shown a prolongation of the period until delivery for women given indomethacin versus women on placebo, but have not shown a significant change in perinatal mortalitay or morbidity. [Blumfeld 2009]

In a meta-analysis done by Haas et al. l58 randomized trials were included with the objective to determine the best first line tocolytic agent. All groups of tocolytics were included. The results showed that all agents were more effective than placebo in delaying delivery. However, COX inhibitors were found to be the best tocolytic agent before 32 weeks of gestation when considering maternal and fetal outcomes [Haas 2009].

### Oxytocin-receptor antagonists

The hormone oxytocin contributes to the production of uterine contractions by indirectly releasing calcium from the sarcoplasmic reticulum via the inositol triphospate second messenger system. Oxytocin-receptor antagonists compete with oxytocin for the binding site on receptors in the decidua and myometrium. It therefore seems logical that ocytocin-receptor antagonists would be an effective tocolytic agent. However in a current meta-analysis where 1695 women participated there was not found any difference in the outcome between the women given the oxytocin-receptor antagonist atosiban and those who received a placebo. Atosiban was however associated with a lower birth weight of the neonate and an increase in death during the first year of life. [Simhan 2007]

## Antibiotics

There is a strong association between infection of the urogenital tract and preterm delivery. Around 80% of premature deliveries are associated with intrauterine infection. [Goldberg (1998)]A proposed mechanism for this is that the production of inflammatory cytokines increases the production of prostaglandins thus increasing the contractility of the myometrium. [Stetzer 2000]. A contribution to the process of prematurely rupturing the membranes is provided by bacteria producing collagenases and proteases that weaken the chorion, and amnion making them more susceptible to an ascending infection [Kenyon 2004]

A commonly accepted theory is that mild subclinical infection of the upper or lower urogenital tract is part of the etiology for many cases of early preterm labor or preterm rupture of membranes. Some of the bacteria commonly considered causative of this are those responsible for causing bacterial vaginosis like G. vaginalis, Mycoplasme, Bacteroides and other vaginal bacteria. A study done in 1986 by Gravett et al. showed that women presenting

with signs of preterm labor who were found to have bacterial vaginosis had a shortened latency period until delivery, and an increased incidence of choriamnionitis. [Stetzer 2000]

Maternal infection appears to be widely accepted as an important risk factor for preterm birth. When considering this it seems natural to expect positive results from treatment with the appropriate antibiotcs. However, studies show contradictory results, with the majority showing no difference in the outcome for women with uncomplicated preterm birth.

Many studies have been performed involving pregnant women with bacterial vaginosis. A review article by Stetzer and Mercer described several of these in an article from 2000. Studies by McGregor et al. in 1994 and by Joesoef et al. in 1995 both evaluated the effect in decreasing preterm birth using topical clindamycin cream to treat women with bacterial vaginosis and neither found there to be any detectable improvement among the women treated. A trial by Haut et al. showed that systemic treatment with metronidazole and erythromycin lead to a decrease in preterm birth from 36% to 26% for women who had tested positive for bacterial vaginosis before the start of the trial. [Stetzer 2000]

Oracle is the name of one of the largest recent trials. This was a multicenter trial containing data from 161 centers on 11.050 women from around the world. The indication for their inclusion to the study was either an episode of premature birth or preterm rupture of membranes (PROM). The women were divided into four groups and received, co-amoxiclav, erythromycin, both antibiotics or placebo for 10 days. The results for women with preterm rupture and those at risk for preterm birth were evaluated separately. ORACLE I [Kenyon2001] presented the results of the patients with PROM and showed that there was an increase in latency in the time until delivery with the use of with both erythromycin and co-amoxiclav. There was also a reduction in chronic lung disease and the need for oxygen therapy in the neonates. However, there was found and increase of necrotizing enterocolitis

with the use of co-amoxiclav. The conclusion was therefore that erythromycin, not co-amoxiclav, should be given to women with PROM. The second part of the trial was presented as ORACLE II. [Kenyon 2001] The patients were given the antibiotics prophylactically during an episode of preterm labor. The results showed no difference in the outcome among the four groups. And the authors concluded that women with this indication should not be given antibiotic unless there were signs of infection.

Preterm rupture of membranes is a strong indication that preterm birth is imminent. Most women who do not receive treatment deliver within a week. [Goldberg 1998].A systematic review by Kenyon et al. [Kenyon 2004] evaluates the administration of antibiotics in treating women with preterm PROM. 19 trials comparing the effect of penicillins, erythromycin or Co-amoxiclav versus placebo were evaluated. The results showed that there was a significant reduction in deliveries within 48 hours and 7 days following treatment with all types of antibiotics compared to the placebo group. There was also a reduction in a reduction in maternal infection and chorioamnionitis. However with the use of co-amoxiclav there was found a significant increase in neonatal necrotizing enterocolitis and the authors conclude that the use of co—amoxiclav for this indications should be avoided.

### Omega-3 Fatty Acids

It has been suggested that the addition of omega 3 fatty acids to the diet can decrease the incidence of preterm birth. The theory is that they suppress the production of certain eicosanoids like the prostaglandins that play a part in the induction of preterm labor.Omega 3 fatty acids thought to shift the production towards that of other non-inflammatory cytokines and weaker eicosanoids.

There have been some studies and trials on the subject where the administration of omega 3 FA have resulted in longer pregnancies and fewer women giving birth prematurely [Spong 2007]

In a recent randomized trial by Harper et al. 852 women with a history of preterm birth were given either an omega-3 supplement or a placebo. The results of this trial showed no difference in the length of the pregnancy or in the outcome for either the mother or the child. [Harper 2010]

### Bed rest

Bed rest, either at home or in hospital, is a commonly recommended treatment for women with various obstetric complaints; preterm delivery is one of these. It is considered by some that hard work and physical activity during pregnancy is a risk factor for preterm birth and so it seems probable that bed rest will improve the outcome of pregnancies for women with a physically demanding lifestyle. Despite its common use there are very few studies that evaluate or support the therapeutic effect of bed rest.

A review article by Goldberg et al. summarizes the effect of bed rest on various conditions that could have a negative effect on the outcome of the pregnancy - hypertension, proteinuric preeclampsia, fetal growth retardation, edema and preterm delivery. There are also potential complications, like thromboembolic disease, muscle atrophy and calcium depletion, from staying in bed. According to the review close to 20% of women who gave birth after 20 week of gestation were at some point during the pregnancy prescribed bed rest as a treatment. The authors concluded that there was not enough evidence to recommend bed rest for any of the indications, except for the hospitalization of patients with proteinuric preeclampsia. They also recommended a drastic reduction in prescribing bed rest for pregnant women, regardless of the indication. [Goldberg 1994]