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Progesterone for the prevention of preterm delivery: an overview

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Abstract

Since the discovery of progesterone, researchers have studied whether administration of exogenous progesterone can prevent preterm birth. Incited by a meta-analysis of trials performed in the 20th century, two trials were published in 2003 that showed a positive effect of progesterone in the prevention of recurrent preterm birth. More recent data cannot support these findings. In multiple pregnancies the use of progesterone does not seem to reduce the number of preterm births. The results in pregnant women with asymptomatic shortening of the cervix are promising, although more research is needed in this group.

Introduction

Of the approximately 175,000 live born children who are delivered after a gestational age of 22 weeks in the Netherlands each year, 7.1% is born before 37 weeks and 1.1% even before 32 weeks.[1] Of these children 3.8 and 21% will decease within 28 days after birth, respectively. A total of 22% of all prematurely born children are admitted to a Neonatal Intensive Care Unit. Preterm birth thus forms one of the largest problems in perinatology and is therefore a continuous topic of interest in scientific research.

At the end of the 1920s, George Corner and Willard Allen discovered the steroid progesterone, which turned out to be one of the most important factors in maintaining pregnancy due to its role in endometrial proliferation. This discovery was ensued by the theory that administration of exogenous progesterone may delay birth. In several animal species, delivery is preceded by a decrease in serum progesterone. In cows and sheep, this decrease is caused by diminished placental secretion; in other mammals the progesterone concentration is reduced due to regression of the corpus luteum.[2] In humans however, where production of progesterone is passed on from the corpus luteum to the placenta in the 12th week of pregnancy, a decrease in serum progesterone cannot be observed. As an explanation for this, Csapo developed the 'see-saw' theory in the 1960s.[3] This theory hypothesizes that there is a relative decrease in progesterone due to an increase in oxytocin and prostaglandins.

After the first trimester, progesterone most likely acts in several ways. In vitro, it has been shown that progesterone has an inhibitory effect on prostaglandins and oxytocin, and that it can decrease the number of oxytocin receptors and gap junctions in the myometrium.[4, 5]

It is a fact that mifepristone, a progesterone antagonist, is effective in inducing abortion.[6] How progesterone suppletion can be effective in preventing preterm birth in pregnant women who already have very high serum progesterone concentrations, remains unclear.

History

The first randomized controlled trials (RCTs) that studied progesterone treatment for the prevention of preterm birth date from the 1960s (table 1).

In these studies, 17-alpha hydroxyprogesterone caproate (17OHPC) was used, a synthetic form of progesterone that has a structure similar to that of medroxyprogesterone acetate (MPA) and is administered through intramuscular injection. In 1990, Keirse et al. published a meta-analysis of the RCTs that were published thus far, leaving out the trial by Hauth which did not study a high-risk population.[7] This analysis yielded an odds ratio (OR) of 0.50 (95% CI 0.30-0.85) for preterm birth before 37 weeks when 17OHPC was used.

Table 1 Randomized trials until the year 2000, studying progesterone administration for the prevention of preterm birth

1st author; year	patient characteristics	intervention at gestational age	n	relative risk (95%-CI) for preterm birth*
Levine; 1964 [28]	3 previous miscarriages	17OHPC 500 mg / week 16-36 weeks	30	0.67 (0.14-3.04)
Papiernik-Berkhauer; 1970 [29]	'high risk'	17OHPC 250 mg / 3 days 28-32 weeks	99	0.22 (0.05-0.83)
Johnson; 1975 [30]	2 previous miscarriages or 1 previous preterm birth	17OHPC 250 mg / week 24-37 weeks	50	0.23 (0.06-0.75)
Hartikainen; 1980 [31]	twin pregnancy	17OHPC 250 mg / week 28-37 weeks	77	1.62 (0.83-3.27)
Hauth; 1983 [32]	women in the military	17OHPC 100 mg / week 16-36 weeks	168	1.10 (0.33-3.47)
Yemini; 1985 [33]	2 previous miscarriages or 2 previous preterm births	17OHPC 250 mg / week 16-36 weeks	80	0.37 (0.15-0.87)

n = number of patients; 17OHPC = 17-α-hydroxyprogesterone caproate. *For each trial the primary outcome was delivery < 37 weeks.

Table 2 gives an overview of randomized trials studying progesterone for the prevention of preterm birth that were published after the year 2000. In 2003, a placebo controlled RCT was published by Meis et al. on women with a singleton pregnancy and a history of one or more spontaneous preterm births.[8] Women who participated in the trial received weekly intramuscular injections of 250 mg 17OHPC or placebo, starting at 16-20 weeks of gestation. Treatment was continued until 36 weeks; the primary outcome measure was delivery before 37 weeks. A total of 463 women were randomized in a 2:1 (17OHPC:placebo) ratio. In the 17OHPC group 36.3% delivered before 37 weeks, versus 54.9% in the placebo group (relative risk [RR] 0.66; 95% CI 0.54-0.81). Similar relative risks were found for delivery before 35 weeks (RR 0.67; 95% CI 0.48-0.93) and 32 weeks (RR 0.58; 95% CI 0.37-0.91). Furthermore, a trend was observed towards less neonatal morbidity in the 17OHPC group.

Table 2 Randomized trials after the year 2000, studying progesterone administration for the prevention of preterm birth

1st author; year	patient characteristics	intervention at gestational age	primary outcome	n	relative risk (95%-CI) for preterm birth
Meis; 2003[38]	≥1 previous preterm births	17OHPC 250 mg / week 20-36 weeks	delivery <37 weeks	463	0.66 (0.54-0.81)
da Fonseca; 2003[39]	≥1 previous preterm births or uterine anomaly or 'incompetent cervix'	progesterone 100 mg vaginally / day 24-34 weeks	delivery <37 weeks	142	0.49 (0.25-0.94)
Rouse; 2007[11]	twin pregnancy	17OHPC 250 mg / week 20-36 weeks	delivery <35 weeks	655	1.2 (0.9-1.5)
Fonseca; 2007[15]	cervix <15 mm at 20-25 weeks	progesterone 200 mg vaginally / day 24-34 weeks	delivery <34 weeks	250	0.56 (0.32-0.91)
Facchinetti; 2007[17]	successful tocolysis	17OHPC 341 mg / 4 days	delivery <37 weeks	60	0.15 (0.04-0.58)
O'brien; 2007[10]	≥1 previous preterm births	progesterone 90 mg vaginally / day 23-37 weeks	delivery <37 weeks	659	1.03 (0.85-1.23)
Borna; 2008[16]	successful tocolysis	progesterone 400 mg vaginally / day	number of days until delivery	70	p-value= 0.037
Caritis; 2009[12]	triplet pregnancy	17OHPC 250 mg / week 20-35 weeks	delivery <35 weeks	134	1.1 (0.8-1.6)
Norman; 2009[13]	twin pregnancy	progesterone 90 mg vaginally / day 24-34 weeks	delivery <34 weeks	247	1.27 (0.91-1.78)

n = number of patients; 17OHPC = 17-α-hydroxyprogesterone caproate.

In the same year, a placebo controlled RCT by Fonseca et al. was published, in which not only pregnant women with one or more previous spontaneous preterm births (94%) were included, but also pregnant women with a uterine anomaly (3%) or an incompetent cervix (3%).[9] The intervention was daily vaginal administration of 100 mg progesterone from 24 to 34 weeks of gestation. In this study 157 women were randomized, of which 142 were eventually analyzed. The relative risks for preterm birth before 37 and 34 weeks were 0.48 (13.8% vs. 28.5%, 95% CI 0.25-0.94) and 0.15 (2.8% vs. 18.6%, 95% CI 0.04-0.56), respectively. After the publication of the trials by Meis et al. and Fonseca et al. there was a renewed worldwide interest in progesterone for the prevention of preterm birth. Since then, multiple RCTs in other high risk groups have been published, or are currently being conducted.

History of preterm birth

As previously mentioned, the trials by Meis et al. and Fonseca et al. from 2003 showed a clear decrease of the number of recurrent preterm births after the use of progesterone and 17OHPC.

In 2007 however, an RCT was published that randomized women with a history of spontaneous preterm birth to either daily vaginal administration of 90 mg progesterone gel of to placebo.[10] No difference was found between progesterone and placebo respectively in the occurrence of preterm birth before 37 weeks (42 and 41%, RR 1.02, 95% CI 0.85-1.23), 35 weeks (23% and 27%, RR 0.85, 95% CI 0.65-1.13) and 32 weeks (10 and 11%, RR 0.91, 95% CI 0.56-1.41).

Multiple gestation

In 2007 the results of an RCT by Rouse et al. were published.[11] In this study 655 women with a twin pregnancy were randomized to 17OHPC or placebo. In the 17OHPC group, women received the same treatment as in the previously mentioned trail by Meis et al. from 2003. The percentage of spontaneous preterm birth was not significantly different between the 17OHPC group and the placebo group (31.2 and 26.1%, RR 1.2, 95% CI 0.9-1.5).

Another trial by the same research group with a similar setup was published in 2009.[12] In this trial 134 women with a triplet pregnancy were included. There was no difference in effect of 17OHPC or placebo on the risk of spontaneous preterm birth before 35 weeks (48 and 43%, RR 1.1, 95% CI 0.8-1.6).

An RCT in twin pregnancies that was published in 2009 did not show a decrease in preterm birth or intra-uterine foetal death before 34 weeks after treatment with daily doses of 90 mg vaginal progesterone between 24 and 34 weeks of gestation (25% in the progesterone group vs. 19% in the placebo group, RR 1.27, 95% CI 0.91-1.78).[13]

During the course of 2010 the results of the Dutch AMPHIA-trial will become available.[14] This RCT studied whether weekly intramuscular injections of 250 mg 17OHPC reduce the risk of neonatal morbidity in multiple pregnancies (twin, triplet and quadruplet). In each participant, cervical length was measured at a gestational age of 20 weeks to determine whether 17OHPC is effective in women with a multiple pregnancy and asymptomatic cervical shortening.

Asymptomatic cervical shortening

Fonseca et al. published a new trial in 2007.[15] In this trial, they performed a transvaginal measurement of cervical length in pregnant women without signs of preterm labour at a gestational age of 20-25 weeks. If cervical length was below 15 mm, the woman was asked to participate in a randomized, placebo-controlled trial, where she would receive daily vaginal doses of 200 mg progesterone or placebo between 24 and 34 weeks of gestation. A total of 24,620 pregnant women underwent cervical length measurement; the cervix was shorter than 15 mm in 413 women (1.7%). Two hundred and fifty women

in this group consented to participation in the trial. The relative risk of spontaneous preterm birth before 34 weeks was 0.56 after use of progesterone, compared to placebo (19.2% for progesterone and 34.4% for placebo; 95% CI: 0.32-0.91). The results also showed a non-significant trend towards less neonatal morbidity and mortality in the progesterone group.

Recently, the Triple P-study has started recruiting in the Netherlands. In this study, asymptomatic pregnant women undergo a transvaginal cervical length measurement at 18-22 weeks, and are asked to participate in a placebo-controlled RCT if cervical length is below 25 mm. The intervention consists of daily vaginal administration of 200 mg progesterone or placebo. The primary outcome is a composite measure of neonatal morbidity, consisting of infant respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage grade 2b or more, necrotizing enterocolitis, proven sepsis and neonatal mortality.

Threatened preterm labour

Two recent studies have investigated whether progesterone can increase time to delivery after threatened preterm labour has successfully been treated with tocolysis.[16, 17] An RCT published in 2007 showed that the percentage of preterm births before 37 weeks was lower in pregnant women who had received 341 mg 17OHPC intramuscularly every four days after a 48 hour treatment with atosiban (16 vs. 57%; RR 0.15; 95% CI 0.04-0.58).[17] In a group of pregnant women that was studied in 2008, the number of days until delivery after 48 hours of tocolysis with magnesium sulphate and subsequent daily vaginal administration of 400 mg progesterone was higher in the progesterone group than in the control group (36.1 ±17.9 vs. 24.5 ±27.2; p=0.037).[16]

It is important to mention that magnesium sulphate is not used as a tocolytic agent in the Netherlands. Neither of the studies was placebo controlled.

Safety

The safety of progesterone treatment during pregnancy has been studied extensively. In three retrospective cohort studies published in the 1980s, a total of 2962 children that had been exposed to 17OHPC, medroxyprogesterone acetate or other progestogens during pregnancy were studied.[18-20] This group was compared with a group of 3550 children of mothers who had not been treated with progestogens. No differences in congenital anomalies were found.

In 2007 the results of a follow-up study on 278 children whose mothers had participated in the trial by Meis et al. in 2003 were published. The average age of the children was 4 years; no differences were found between children of mothers in the 17OHPC group and children of mothers in the placebo group with respect to congenital anomalies, physical health and behavioural problems.[21]

A retrospective cohort study from 2007 indicated that treatment with 17OHPC increases the risk of gestational diabetes (12.9 vs. 4.9%; OR 2.9; 95% CI 2.1-4.1).[22] These

results are contradicted by a secondary analysis of the trials by Meis et al. and Rouse et al. which reports no increased incidence of gestational diabetes after treatment with 17OHPC in either singleton or twin pregnancies.[23]

Discussion

Although there are implications for a possible beneficial effect of exogenous progesterone administration on the prevention of preterm birth, no clear conclusion can be drawn based on the available literature.

A possible explanation for the conflicting results that have been found until now is that the cause of preterm birth is multifactorial. It is not only the balance in pregnancy related hormones that plays a role, but also inflammation, ischemia and anatomical anomalies. Often there is a combination of factors at work, which has lead to the use of the term "preterm labour syndrome" in the literature. This complex aetiology makes it difficult to develop preventive treatment strategies and to select the right target group for a certain treatment. The latter is also hindered by the fact that the majority of spontaneous preterm births occur in pregnant women without previously established risk factors.

In the past studies have assessed whether preterm birth could be prevented by bed rest, cervical cerclage and monitoring of the uterine activity. A 2004 Cochrane review, including only one RCT, did now show any difference in preterm births between women having been prescribed bed rest and a control group (RR 0.92; 95% CI 0.62-1.37).[24] An individual patient data meta-analysis published in 2007 did not show a significant difference in gestational age at delivery between women with a singleton pregnancy who had been treated with a cervical cerclage and those who had not, regardless of the indication; the authors concluded that more research is needed to draw a clear conclusion on the effectiveness of this treatment.[25] In the cerclage group, there were more cases of fever (6.2 vs. 2.6%, OR 2.35; 95% CI 1.37-4.05. In women with a twin pregnancy, cerclage even had a detrimental effect on perinatal mortality and miscarriages (OR 5.88; 95% CI 1.14-30.19). A meta-analysis from 1995 showed that home monitoring of the uterine activity reduced the number of preterm births (RR 0.76; 95% CI 0.59-0.98), but this had no effect on neonatal outcome.[26]

In March 2007, the guideline "Prevention of recurrent spontaneous preterm birth" was issued by the Netherlands Organisation for Obstetrics and Gynaecology. This guideline mentions as one of its key recommendations that the effectiveness of progesterone in the prevention of preterm birth should be discussed with women with a history of spontaneous preterm birth before 34 weeks. An inventarisation during the second half of 2007 showed that at that time, only 25% of the interviewed Dutch gynaecologists applied progesterone treatment for the prevention of preterm birth in practice.[27]

The long history of 17OHPC treatment and the results of the follow-up of children from the trial by Meis et al. make it sufficiently convincing that administration of 17OHPC during pregnancy is not harmful for the child. Opportunities for long term follow up of children in future trials should however not remain unused. Special focus on a potentially elevated glucose intolerance as a result of 17OHPC treatment is also recommended, as the findings on this subject are conflicting.

Conclusions

So far, progesterone seems to be the most promising treatment in the prevention of preterm birth. In the literature, asymptomatic cervical shortening, is the only risk factor for which a univocal beneficial effect is found. However, in view of the uncertain theoretic background of the mechanism of action of exogenous progesterone, the fact that only one trial on women with asymptomatic cervical shortening has been published and the limited reports on neonatal outcome so far, more studies are needed to establish treatment effects and side effects. In addition, more research should be conducted into the optimal administration and dosage of progesterone. It is preferable to restrict treatment with progesterone for the prevention of preterm birth to trial settings. International trial registers show that multiple studies are being conducted into progesterone for the prevention of preterm birth worldwide. The now finished AMPHIA trial and recently started Triple P-study in the Netherlands will contribute to answer to this question.

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