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General discussion

Progesterone for the prevention of preterm birth: the long awaited remedy for a major obstetric problem or a large-scale consumer of research funding with little chance of success? With conflicting trial results and disputable biological plausibility, the question is still open for debate.

History of preterm birth

The publication of the trial by Meis in 2003 that proved to be the motive for many subsequent studies on progesterone as a preventive treatment for preterm birth, was accompanied by an editorial titled: 'Progesterone and preterm delivery – déjà vu all over again'.[1, 2] Although the title of this editorial has a rather sceptical ring to it, the text itself strikes a more optimistic note, concluding that "17P [17-alpha hydroxyprogesterone caproate] may be only the first in a series of successful interventions to reduce the rate of preterm delivery". This statement can be interpreted as both a recommendation for the use of 17P in clinical care and an encouragement for further research on the subject.

Following the publication of the trial by Meis and a similar one by da Fonseca in the same year, twelve obstetric clinics in the Netherlands initiated the application of 17OHPC treatment in clinical practice.[2, 3] All patients treated in the following three years were registered. This registration showed that only a fraction of women with a singleton pregnancy and a history of preterm birth were actually treated with progesterone.

Motivated by this finding, we conducted a study on the application of new and established treatment strategies for the prevention of recurrent preterm birth in the year 2006. We found that treatment with progesterone was offered to 43% of eligible patients and applied in only 29%, and that treatment was offered considerably more often in academic hospitals than in non-academic hospitals. This led to the conclusion that, in the absence of a national guideline, recently published findings are more readily implemented in academic hospitals. Another interesting finding in our study was that in only 67% of patients to whom progesterone treatment was offered, this treatment was actually carried out.

We set out to find reasons for not offering or not administering progesterone treatment by conducting a questionnaire study. We interviewed obstetricians, midwives and women with a previous preterm birth and a current pregnancy or a desire to become pregnant in the future. The results showed that absence of progesterone treatment in protocols and guidelines and unfamiliarity with this treatment were the most important reasons for not offering, accepting and executing progesterone treatment. Lack of belief in the effectiveness of this intervention was generally not an issue.

The lack of doubt on the effectiveness of progesterone treatment in Dutch obstetricians who were familiar with the treatment, was not shared by all internationally. In contrast with the editorial accompanying the Meis publication in 2003, a commentary on both

the Meis and da Fonseca trials in *Birth 2004,* was considerably less praising.[4] The commentary titled 'Progesterone and Preterm: Seventy Years of 'Déjà Vu' or 'Still To Be Seen'?' was written by the author who had also published a meta-analysis on 17P for the prevention of preterm birth in 1990 that largely motivated both trials.[5] Proving not to be a relentless and uncritical believer in the effectiveness of progesterone, the author rather convincingly exposes several flaws in the methodology and reporting of both trials, concluding that "Critical analysis of the reports provides no convincing evidence that either one of these treatments [intramuscular 17P or vaginal progesterone] is worth pursuing outside the context of controlled research to determine, first, whether and, second, how the treatments might work".

In 2007, a guideline for the prevention of recurrent spontaneous preterm birth was issued by the Netherlands Society for Obstetrics and Gynaecology (NVOG). A national guideline for this indication did not exist until that time. In the guideline it is stated that "the effectiveness of progesterone treatment should be discussed with any pregnant woman with a history of spontaneous preterm birth before 34 weeks". Although this statement supports practitioners in applying progesterone treatment, it also reflects some doubt on the effectiveness among the drafters of the guideline. The Dutch results of 17P treatment for the prevention of recurrent preterm birth might aid in formulating a more explicit recommendation. In a matched cohort study, we set out to compare the pregnancy outcomes of women treated with progesterone to those of a group of historical control subjects. Unfortunately, matching patients who received treatment after initiation in 2003 with women who had delivered before that time, proved to be extremely difficult due to limited data in the Dutch Perinatal Registration. We were able to find matching control subjects for only 56 registered patients. In this group, the recurrence risk of preterm birth before 37 weeks was 43% after treatment with 17P and 34% without such treatment. No statistically significant differences were found in gestational age at delivery, number of preterm births before 32 and 35 weeks, perinatal mortality and neonatal admission. Although the numbers in this study are small, they support the notion that universal progesterone treatment in all women with a singleton pregnancy and a history of preterm birth can for the present not be considered 'evidence based medicine'.

In 2009 a Cochrane systematic review and meta-analysis was performed on the studies that had been published thus far.[6] For the population of women with a history of spontaneous preterm birth and the outcome "preterm birth less than 37 weeks", four studies were included. Two of these studies used vaginal progesterone, while the other two used intramuscular progesterone. Three studies showed a marked reduction of recurrent preterm birth after treatment with progesterone. However, the most recent study out of these four shows no effect of (vaginal) progesterone treatment.[7] In the meta-analysis, this causes the beneficial effect of vaginal progesterone to disappear, while the overall effect of progesterone for this indication and outcome is reduced to a risk ratio of 0.80 (95% CI 0.70-0.92). More study results will be published in the near

future, as several trials on progestogens for the prevention of recurrent preterm birth are still recruiting. Some of these trials will focus on comparing vaginal progesterone to intramuscular dosage forms. Whether the beneficial effect of progesterone that was shown in the 2009 Cochrane review will remain significant, diminish further or will be extinguished altogether when more trial data are added, remains to be seen.

Multiple gestation

Infected by the progesterone virus that spread in 2003, our study group set up a randomized, placebo-controlled trial to find out whether 17P could reduce adverse neonatal outcome in children born from multiple pregnancies. A composite measure of adverse neonatal outcome was present in 16% of children born to mothers in the 17P group, and in 12% of children in the placebo group. The mean gestational age at delivery was similar for the 17P group and the placebo group. Treatment with 17P did not reduce the delivery rate before 28 weeks, 32 weeks, or 37 weeks of gestation. A mid-trimester cervical length measurement in participating women yielded an insufficient number of women with a cervix below 25 mm to draw any conclusions on the effect of 17P in this group.

During the inclusion period of the trial, it turned out that a progestogen epidemic had developed; multiple research groups all over the world were now studying the effects of 17P or vaginal progesterone in women at risk of delivering preterm. Approaching other trial groups has lead to an individual patient data meta-analysis on nine trials in multiple pregnancies so far. Preliminary analysis on the 6,608 children born to mothers included in these trials shows no effect of progestogens on adverse neonatal outcome in twin pregnancies (RR 1.05; 95% CI 0.91-1.2). There is a potential effect in the 55 women in this meta-analysis with a cervical length below 25 mm in the second trimester, but the numbers were again too small to reach statistical significance (41% vs. 61%; RR 0.67; 95% CI 0.40-1.1).

Short cervix

Could it be that the key to the success of progesterone treatment lies in women with asymptomatic cervical shortening? Two large trials in singleton pregnancies are strongly pointing in that direction. The first trial was published in 2007 and enrolled 250 women with either a singleton or multiple gestation who had a cervical length below 15 mm without signs of preterm labour at a gestational age of 20-25 weeks.[8] Participants were randomized to either daily vaginal doses of 200 mg progesterone or placebo. The relative risk of spontaneous preterm birth before 34 weeks was 0.56 after use of progesterone. The results also showed a non-significant trend towards less neonatal morbidity and mortality in the progesterone group. The second study was published in 2011 and randomized 465 women with a cervical length between 10 and 20 mm at 19–24 weeks' gestation to either 90 mg progesterone in bioadhesive gel or a placebo gel transvaginally daily.[9] Progesterone caused a significant reduction in deliveries <

33 weeks (RR 0.55) and < 28 weeks (RR 0.50) compared to the placebo group. In the treatment group there was also a significant reduction in adverse neonatal outcome (RR 0.57). More trials with a similar design are currently recruiting, among which is the Dutch Triple P study.[10] So far, the findings of the two mentioned trials have not been contradicted and their methodology seems valid.

Women with a singleton gestation and asymptomatic cervical shortening have repeatedly been shown to have an increased preterm birth risk. We performed a systematic review and bivariate meta-analysis on the accuracy of cervical length for predicting preterm birth in asymptomatic women with a multiple pregnancy and found 21 studies reporting on 2757 women. Although there was a large variation in gestational age at measurement, cut-off point for cervical length and definition of preterm birth, the summary ROC curve indicated a good predictive capacity of short cervical length for preterm birth.

Progesterone treatment in women with a multiple pregnancy and asymptomatic cervical shortening in the second trimester has thus far not been studied extensively. Although a secondary analysis of our trial in multiple pregnancies showed that 17P had no effect on the rate of cervical shortening during pregnancy, the positive results in women with a singleton pregnancy and a short cervix and the potentially beneficial effect seen in analyses of short cervix subgroups in multiple gestation trials, may give incentive for future research in this specific risk group.

Safety

Hormone treatment during pregnancy has been under intense scrutiny since the diethylstilbestrol drama. Several retrospective studies on the safety of progestogen treatment during pregnancy show no increased risk of congenital anomalies.[11-13] In a follow-up study on children whose mothers had participated in a large 17P trial, no differences were found between children born in the 17P group and children born in the placebo group with respect to congenital anomalies, physical health and behavioural problems.[14]

A retrospective cohort study from 2007 indicated that treatment with 17P increases the risk of gestational diabetes, but this has been contradicted by a secondary analysis of two randomised trials which showed no increased incidence of gestational diabetes after treatment with 17P.[15, 16] Although research so far indicates that progestogens are safe for both mother and child, researchers and clinicians should remain careful not to assume that progestogens will never 'hurt to try'.

Biological plausibility

Summarizing the current literature and the findings reported in this thesis, it seems that progesterone is very likely to be effective in preventing preterm birth and subsequent adverse neonatal outcome in women with asymptomatic cervical shortening. For these

trial results to be truly convincing, one remaining question needs to be answered: How does progesterone work?

To a certain level, the need for progesterone to sustain gestation seems perfectly logical. Facts are that progesterone is an important factor in maintaining pregnancy and that suppletion improves implantation and pregnancy rates in IVF treatment.[17] Another fact is that mifepristone, a progesterone antagonist, is effective in inducing abortion.[18] Some in vitro studies have 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.[19, 20] From this point forward however, facts are replaced by theory which may turn out to be fiction.

The lack of a clear starting point on which any treatment for preterm delivery is likely to be based, is largely due to the complicated nature of the condition itself. The designation 'preterm labour syndrome' reflects the heterogeneous nature of the problem. Inflammatory processes are an indisputable part of this syndrome, but whether as a cause or consequence remains an unsolved 'chicken or egg' dilemma. There are indications that the local production of pro-inflammatory cytokines is the first link in a chain of events that lead to effacement of the cervix. Cervical shortening would then be a symptom of a process already in motion, thus making progesterone a rescue treatment rather than a preventive one.

Perhaps the most unsatisfying lack of support for the effectiveness of progesterone treatment is that no difference in serum progesterone levels can be found between women delivering preterm and those who deliver at term.[21] This makes finding the right dosage form, frequency and amount a matter of guessing, trial and error.

Recommendations for clinical practice

The research presented in this thesis was not focused on in vitro or laboratory science, but on clinical evaluation. The actual question may not be whether progesterone is an effective treatment or not, but at what point we allow ourselves to be convinced by results generated by clinical trials in the absence of biological plausibility. In today's research climate, where the generation of positive results still attributes to a researchers status and publication bias is all but extinct, we should remain very critical.

A positive effect of progestogen treatment in women with a previous preterm birth seemed to be firmly supported by trial results in 2003, but is now under debate due to conflicting evidence. The same could prove to be true for treatment in women with a short cervix. The currently available evidence is therefore insufficient to promote progestogen treatment beyond the realm of research. The progress and results of progestogen studies that are now recruiting should be observed carefully. If initial positive trial results are confirmed by more than one study group in large numbers, recommendations can be included in guidelines and new starting points may be found for further research. Until that time, patients should be encouraged to participate in ongoing trials. In case of asymptomatic cervical shortening in the second trimester and ineligibility for trial

participation, progestogen treatment can be justified based on the available evidence, but only after clear counselling on the uncertainty of that evidence. In all other patients with an increased risk of preterm birth, progestogen treatment should not be applied outside of research settings.

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