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A brief guideline proposal for using dydrogesterone prevention or treatment of pregnancy disorders

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Introduction

Only certain progestogens are to be used for pregnant women.

Dydrogesterone is one of the progestogens, which are suitable to be applicated in pregnancy [1].

The following progestogens had been studied:

1. Dydrogesterone (oral)
2. Micronized progesterone (vaginal)
3. 17- Hydroxyprogesterone caproate (intramuscular)

Only dydrogesterone will be considered in this mini review.

All studies with dydrogesterone have been successful looking at threatened miscarriage, recurrent (habitual) miscarriage, preterm labour and preeclampsia provided organic lesions such as myoma or uterine septum have been removed.

In addition, one has to differenciate whether the progestogen is used for prevention or therapy.

The dose used for prevention or treatment has been gradually increased for dydrogesterone and micronized progesterone and the length of time to be used has been extended [2,3].

Threatened miscarriage

At present, the situation is the following:

Threatened miscarriage is defined as vaginal bleeding, closed cervix and intact fetus by ultrasound.

The pregnant woman receives treatment with dydrogesterone p.o. giving 40 mg at once and thereafter up to 40 mg/d (2 x 20 mg) orally. This should be continued until the 37th week of gestation.

Why? It was shown by several publications that women with threatened miscarriage later in pregnancy have higher incidence of preterm labour or preeclampsia, bleeding problems and small for date babies [4-6].

In one of our studies on prevention of preeclampsia using dydrogesterone only up to 16 weeks of gestation, the rate of preterm labor was similar as in the control group, while the incidence of preeclampsia was significantly reduced ($p<0.001$) [7].

Conclusion

In threatened miscarriage therapy should be done by dydrogesterone 40 mg p.o. at once and thereafter 2x20 mg/d until 37 weeks of gestation.

Recurrent (habitual) miscarriage

Less frequent but by no means less important is the use of dydrogesterone in women with recurrent (habitual) miscarriage.

Recent large randomized studies using on the one hand dydrogesterone 20 mg/d up to 20 weeks of gestation [8] and on the other hand a raised dose of micronized progesterone intravaginally of 2 x 400 mg/day up to 12 weeks of gestation [9]. The data for dydrogesterone were leading to a significant reduction of miscarriage, while in the progesterone study there was no significant difference compared with the control group. The rate of life birth was in the progestogen group 65.8% and for the placebo group 63,3% (not significant) [9].

Conclusion

Dydrogesterone 2 x 20 mg/d should be used in pregnant women with a history of recurrent (habitual) miscarriage and extended up to 37 weeks of gestation.

Preterm labour

In 1990 a metaanalysis of the use of 17-α hydroxyprogesterone caproate concluded that a significant reduction of preterm birth and a significant improvement of fetal outcome can be accomplished [10].

But no real practical consequences were drawn. Thereafter, studies with micronized progesterone vaginally (100 to 200 mg/d) were used to demonstrate a favourable effect regarding the prevention of preterm labour [11,12].

In addition, to prevent preterm labour in pregnant women with a history of spontaneous preterm labour and preterm delivery could be shown in women with a short cervix [13].

Recently, the effectiveness of micronized progesterone vaginally could not be verified [14].

Publications on dydrogesterone and prevention of preterm labour are limited [15,16]

My own unpublished data with dydrogesterone 2 x 20 mg/d orally and continuously until 37 weeks of gestation where successful. However, further studies are needed.

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Treatment of preterm labour with progestogens

When contractions are present, but amniotic membranes are intact, the use of dydrogesterone can stop labour together with a tocolytic or without.

Own unpublished data and results of others have verified this [15,16]

Conclusion

1. The use of dydrogesterone (2 x 20 mg/d p.o.) appears to achieve preterm labour/ preterm birth prevention when used from the 16th week of gestation until 37 weeks of gestation. This was shown for a history of previous preterm birth and or a short cervix.
2. Treatment of preterm labour without rupture of the amniotic membranes can be accomplished with 2 x 20 mg dydrogesterone daily with or without tocolytic drugs.

Prevention of preeclampsia

Progesterone has been shown to lower systolic and diastolic blood pressure in women and men [17].

Already in 1957 it was reported that with progesterone i.m. the full clinical picture using intramuscular progesterone could be favourable improved [18,19].

The infants of the progesterone treated women appeared to have improved brain function [19].

However, this was discussed, but no further studies have been published.

Later in 1971 and 1982 successful treatment of preeclampsia with progesterone was done, but no further studies have been published [17,20].

In 2014 a prospective, randomized, placebo-controlled trial was published, revealing that dydrogesterone 30 mg/d p.o. starting within the first 5 days after ovum pick-up until 16 weeks of gestation did lead to a highly significant reduced development of preeclampsia ($p<0,001$), incidence 1,7%, in the prevention group and 12,9% in the control group [20].

Dydrogesterone was started in the first five days after ovum pick-up through 16 weeks of gestation.

Looking at other disturbances, like preterm labour, no difference was found [20], when compared with the control group [20]. This fits very well with the clinical findings of achieving preterm labour prevention by treating with a progestogen from the 16th to the 37th week of gestation.

In the meantime, a retrospective study was done with women having ART-treatment and taking dydrogesterone or dydrogesterone/ 17-α hydroxyprogesterone caproate in the same country [21]. Again, a significant reduction of preeclampsia was encountered using the hormone treatment up to 14-16 weeks of gestation ($p<0.05$) [21]. There was no difference between the dydrogesterone group and dydrogesterone/17-α hydroxyprogesterone caproate group (6,9% versus 9,9%; $p=0.2$) [21].

A favourable effect of dydrogesterone has also been reported for 30 mg dydrogesterone from early pregnancy until 37th week of gestation in a high-risk woman for preeclampsia prevention [22].

Conclusion

At present, it appears that early use of dydrogesterone (2 x 20 mg/d up to 16th week of gestation) prevents the development of preeclampsia highly significant. A continuation up to 37th week of gestation might further improve the effect and is also effective for prevention of preterm labour.

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