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Progestogens and Pregnancy

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Progestogens and Pregnancy

A. E. Schindler

Based upon the intensive research by E. Diczfalussy and his scholars with the concept of the “feto-placental-unit”, the development of diagnostic procedures by hormone measurements in pregnancy, therapeutic and preventive effects of the use of progestogens (progesterone, dydrogesterone, 17- α -hydroxyprogesterone caproate) were developed and are at present to be further evaluated in order to be used for prevention and treatment of pregnancy disorders such as threatened miscarriage, recurrent (habitual) miscarriage, preterm labor and preeclampsia (hypertension in pregnancy). **J Reproduktionsmed Endokrinol Online 2015; 12 (4): 377–9.**

Key words: Pregnancy, feto-placental-unit, progesterone, dydrogesterone, 17- α -hydroxyprogesterone caproate, threatened miscarriage, recurrent (habitual) miscarriage, preterm labor, preeclampsia (hypertension in pregnancy)

■ Introduction

Going back to the 1960s, extensive basic and clinical studies have been done by Egon Diczfalussy and his research team composed of many scholars from all over the world working at Karolinska Institute in Stockholm. The concept of the “feto-placental-unit” had been established.

Independently we have looked at the isolation, identification and quantitation of steroids in human amniotic fluid [1, 2]. Thereby we could establish for the first time that clinical conditions of the pregnant woman and the fetus such as Rh-sensibilisation did reflect its effect on steroid concentrations in amniotic fluid but also in urine and blood such as estriol as main product of the “feto-placental-unit” [1–5].

■ Progestogens

Since the isolation, identification and quantitation of progesterone some limited attempts have been done to point to the significant role of progesterone in pregnancy over time.

Already in 1957, studies indicated a favourable influence of progesterone on the development of preeclampsia [6]. A real step forward for the peculiar levels of pregnancy were done by Czapo and co-workers, who demonstrated for the first time the success of progesterone for the proper development of pregnancy by removing the corpus luteum around seven weeks of gestation, which did lead to miscarriage and progesterone supplementation avoided this [7]. Indeed, in

pregnancy regarding progesterone the so-called luteal-placental shift occurs, where some lowering of the plasma progesterone was found after seven weeks of gestation, which correlates with the manifestation of threatened miscarriage. Indeed a correlation of the circulating plasma progesterone values and the probability of pregnancy disturbances has been found [8].

Parallel to these experimental situation clinical studies have contributed to the knowledge and understanding of the wide range of actions of progesterone beginning preconceptional and continue throughout pregnancy:

1. Secretory transformation of the endometrium and decidualisation
2. Increase of blood flow
3. Regulation of the extravillous trophoblast invasion
4. Control of uterine contractions
5. Maintenance of cervical rigidity and closure
6. Regulating Th1-cytokines (proinflammatory) and Th2-cytokines (anti-inflammatory)
7. Production of progesterone-induced blocking factor (PIPF) controlling the immune system of the mother in order to protect the semi-allogenic fetus

Systematic clinical studies started in the 1980s. The following clinical entities became subject of investigations:

- Threatened miscarriage and recurrent (habitual) miscarriage
- Preterm labor and preterm birth
- Preeclampsia (hypertension in pregnancy)

The following progestogens were used:

- Progesterone (micronized) (i. m., oral, vaginal)
- Dydrogesterone (oral)
- 17 α -hydroxyprogesterone-caproate (i. m.)

■ Threatened Miscarriage and Recurrent (habitual) Miscarriage

The clinical studies started in the 1980s and systematic evaluation was mainly done with dydrogesterone. One can assume that similar to dydrogesterone progesterone has been used with limited published evaluations.

From the prospective, randomized studies with dydrogesterone a recent meta-analysis has given the following results with the company proposed treatment recommendation: in threatened miscarriage 40 mg p. o. at the beginning and thereafter 20 mg (2 $\times$ 10 mg) daily. The length of treatment was on average 12 weeks. The results in 660 patients being treated with dydrogesterone in a comparative way was revealing the following results: Dydrogesterone treatment groups 13% miscarriages; Control groups 24% OR 0.47; 95-CI: 0.31–0.71 [9].

■ Recurrent (habitual) Miscarriage

In these cases, it was demonstrated that there are already low progesterone values in the corpus luteum phase in the non-pregnant state in women with a history of recurrent (habitual) miscarriage. In addition, in such cases the cellular

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progesterone receptors were very low [10].

The treatment scheme with dydrogesterone is the same as with threatened miscarriage. The significant clinical effect could be accomplished. Most recent studies have confirmed this [11, 12].

■ Preterm Labor

Delivery before the beginning of week 37 of gestation is defined as preterm birth. The frequency differs from country to country, but even be > 12% like in the USA [13]. The incidence of preterm birth in the developing countries is even higher than in the developed countries [14].

Nationally and internationally preterm birth rate has a trend to rise, it is most costly and is the main problem in obstetrics [15].

Preterm birth is associated with:

1. Main cause of perinatal mortality
2. Main cause of perinatal morbidity
3. High care costs.

The causes for preterm labor/preterm birth are manifold: stress caused by different entities (death of relatives, family struggles, financial problems etc [16]. The stress situation seems to go along with a decrease of circulating progesterone, which was found to be associated with low progesterone throughout pregnancy [17]. Up to now, studies have clearly demonstrated the possible effect of 17 α -hydroxy-progesterone-caproate 250 mg i. m. weekly starting around week 16–37 of pregnancy [18].

A metaanalysis looking at papers using 17 α -hydroxy-progesterone-caproate has already been published in 1990, showing significant reduction of preterm birth compared with the control group [19]. Thirteen years later a large randomized, placebo-controlled investigation showed similar significant results [20]. Further details are described elsewhere [18].

Also in 2003 the use of vaginal progesterone for prevention of preterm labor with 100 mg/200 mg vaginally daily has been published [20].

These results were recently confirmed in a large meta-analysis [21]. Two indications have been investigated:

1. History of previous preterm birth
2. Short cervix

More recently also dydrogesterone has been studied for stopping preterm labor [22].

Our own unpublished results point to two indications for the effective use of dydrogesterone in case of labor:

1. Prevention starting dydrogesterone at week 16 of gestation with 40 mg dydrogesterone and thereafter 2 $\times$ 20 mg daily up to week 37 of gestation.
2. Treatment in case of established labor, perhaps with short cervix but intact membranes 40 mg p.o.; thereafter 2 $\times$ 20 mg daily up to week 37 of gestation or preterm delivery [23].

It also has been suggested to use tocolytics together with progestogens, which saves finally the amount of tocolytics to be used.

■ Preeclampsia/Hypertension in Pregnancy

It is known that progesterone with its anti-mineralocorticoid action can lower the systolic and diastolic blood pressure and this effect was demonstrated in women and men alike [24]. Indeed, clinically established preeclampsia could be controlled with intramuscular progesterone [24, 25].

Before the first reported trial with progesterone in women developing signs of hypertension in pregnancy intramuscular progesterone was used and published in 1957. There was less weight gain and the incidence of preeclampsia decreased considerably [26]. This was confirmed by a later study [27].

In 2014 it was first time published the possibility of prevention of preeclampsia (hypertension in pregnancy) using dydrogesterone in women under ART-procedures receiving 30 mg dydrogesterone p. o. daily starting day 1–5 after ovum pick-up and continued after positive HCG-test up to week 16 of gestation. It was demonstrated in this randomized study that a significant reduction of

preeclampsia (hypertension in pregnancy) could be obtained ($p < 0.001$) [28].

■ Conclusion

Egon Diczfalusy and his scholars have laid the ground work on the understanding of the endocrinology of pregnancy including the concept of the “feto-placental-unit”. This was followed by using hormone measurements in urine and blood to evaluate functional integrity of pregnancy.

At present, the use of progesterone and dydrogesterone have gained great clinical importance creating for reproductive medicine, obstetricians and perinatology the possibility to prevent or treat pregnancy disorders such as threatened miscarriage, recurrent (habitual) miscarriage, preterm labor and preeclampsia.

■ Conflict of Interest

The author declares no conflict of interest.

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