The role of dydrogesterone in recurrent (habitual) abortion

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Abstract

The published evidence regarding the administration of dydrogesterone in the treatment of habitual abortion is summarised in this review. Habitual abortion is defined as the loss of three or more consecutive pregnancies without known maternal or foetal pathology. The immunology of early pregnancy seems to determine the rejection or non-rejection of the allogenic embryo. When peripheral mononuclear cells from recurrent aborters are incubated with progesterone or dydrogesterone in vitro, T-helper (Th)2 cytokines such as interleukin (IL)-4 and IL-6 markedly increase whereas the Th1 cytokine interferon-γ decreases. Additionally, both progesterone and dydrogesterone are thought to inhibit the activity of natural killer cells at the foeto-maternal interface in humans. Progesterone-induced blocking factor (PIBF) mediates the immunological effects of progesterone and dydrogesterone in pregnancy. It affects various phases of the maternal immune response involving both the cellular and humoral immune system, exerts anti-abortive effects and inhibits the release of arachidonic acid. It also favours the production of so-called asymmetric, pregnancy-protecting antibodies. In rodents, blockade of this factor results in the termination of pregnancy and in women considerably lower levels are found in those with threatened abortion or pre-term labour. In order to draw final conclusions as to the usefulness of dydrogesterone in women with a history of recurrent miscarriage, further controlled, blinded, randomised clinical trials are needed.

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1. Introduction

Dydrogesterone belongs to the “retrosteroid” class and is a stereoisomer of natural progesterone. Its conformation is induced by exposing progesterone to ultraviolet light, a reaction first described in the 1950s by Reerink et al. who also discovered this new class of functionally active “retrosteroids” [1]. Dydrogesterone shares similar biological properties with natural progesterone and has high affinity for progesterone receptors (PRs). In contrast to progesterone, dydrogesterone is highly bioavailable after oral intake and is therefore available on the market as an orally active progestogen (Duphaston®). Progesterone was recognised early on to be one of the most important steroids required for the maintenance of pregnancy, and so dydrogesterone became a candidate for the treatment of threatened and habitual abortion. As early as the beginning of the 1980s, the pregnancy-maintaining effects of dydrogesterone were demonstrated in ovariectomised rats, although the underlying mechanism was unknown [2]. In contrast to other progestogens on the market, dydrogesterone has no relevant androgenic or anti-androgenic activity on the foetus and can therefore be safely administered to mothers without the risk of causing foetal genital malformations. In this review, we summarise the published evidence regarding the administration of dydrogesterone in the treatment of habitual abortion.

2. Habitual abortion

Habitual abortion affects ≤1% of women. It is defined as the loss of three or more consecutive pregnancies without known maternal or foetal pathology. The risk of having another abortion after three consecutive abortions is as high as 55% [3]. Because of the lack of recognised causes for this condition, the treatment of affected women poses serious problems for gynaecologists. In general, miscarriage can be induced by multiple factors such as chromosomal abnormalities of the foetus or severe malformations, maternal uterine malformations, intrauterine infections, endocrine factors and...
hormonal defects, coagulation disorders and some chronic medical conditions.

Why an embryo is rejected by the mother after exclusion of the above factors remains speculative in most cases and many theories have emerged over the years [4]. A field of special interest, and perhaps the key to understanding habitual abortion, is the immunology of early pregnancy that seems to determine between rejection or non-rejection of the allogenic embryo. Progesterone is endowed with immunological properties. Chronic exposure of immunocompetent maternal cells to allogenic embryonic antigens progressively increases the number of PRs on maternal lymphocytes, whereas cases of spontaneous abortion and pre-term labour are associated with decreased numbers of maternal PR-positive immune cells [5-8]. However, the expression of the PR protein seems to depend on the activation status of the individual lymphocyte. Moreover, emerging evidence indicates that factors interfering with blood coagulation play an important role in the success or spontaneous abortion of an early pregnancy. The presence of the fibrinogen-related procoagulant FgII in trophoblast and villous stroma, for instance, might serve the evolutionary important purpose of attenuating bleeding into and from the foetus. In cases of external danger, such as infection or stress, it appears that the same mechanism that interferes with blood coagulation play an important role in the maintenance of pregnancy. Soon after fertilisation, the early embryo signals to maternal immune cells inducing a shift in cytokine production towards Th2 [13]. A Th1 bias has also been observed in pre-term labour, premature rupture of membranes and pre eclampsia [23,24]. When peripheral mononuclear cells from recurrent aborters are incubated with progesterone or dydrogesterone in vitro, Th2 cytokines such as interleukin (IL)-4 and IL-6 markedly increase whereas the Th1 cytokine interferon (IFN)γ decreases [25].

In addition, both progesterone and dydrogesterone are thought to inhibit the activity of natural killer (NK) cells at the foeto-maternal interface in humans. During the first trimester of pregnancy, CD56+ NK cells comprise a large proportion of decidual lymphocytes. There is evidence from cytotoxicity assays that decidual NK cell activity is significantly less in normal pregnancy than in anembryonic pregnancy and recurrent spontaneous abortion [26]. One of the mechanisms by which NK cells attack their targets is exocytosis of perforin and serin esterase-containing granules. At the time of parturition, the expression of perforin is significantly higher than in the first trimester, indicating suppressed NK activity in early pregnancy. The NK cell suppression, i.e. inhibition of perforin liberation, is in part mediated via a 34 kDa protein that is produced by CD56+ decidual cells and named progesterone-induced blocking factor (PIBF) [27].

4. Progesterone-induced blocking factor

PIBF mediates the immunological effects of progesterone in pregnancy. Its production by lymphocytes is induced by both progesterone and dydrogesterone in a dose-dependent manner and can be inhibited by equimolar concentrations of RU-486 (mifepristone) [28]. PIBF affects various phases of the maternal immune response involving both the cellular and humoral immune system, exerts anti-abortive effects and inhibits the release of arachidonic acid [29]. It induces an approximately eight-fold increase in the production of the Th2-type cytokine IL-10 by activated lymphocytes by stabilising IL-10 mRNA. In mice, lack of PIBF resulted in an
increase in NK activity and IFNγ production, whereas the IL-10 concentration declined [30,31].

PIBF also favours the production of so-called asymmetric antibodies [32], the generation of which seems to be a required immunological alteration for the maintenance of normal pregnancy. Asymmetric antibodies do not possess effector functions and are unable to engender cytotoxic responses to embryonic antigens. Their unique characteristics are consistent with a possible role as “blocking antibodies” that compete with precipitating antibodies of the same specificity, thus helping to control the equilibrium of maternal anti-embryonic immune responses. In the rat model, most anti-paternal antibodies eluted from the placenta are asymmetric [33]. The asymmetric structure is achieved by a mannose-rich oligosaccharide residue on one of the Fab antigen-binding arms. Inhibiting the effects of progesterone by receptor blockade, or neutralising PIBF effects with a specific antibody, significantly reduced the production of asymmetric antibodies in mice [30]. According to a recent study, women with a history of recurrent abortions have significantly lower proportions of asymmetric IgG antibodies (3% of total IgG) compared with healthy pregnant women (29% of total IgG), nulliparous and multiparous women. In addition, amongst antibodies reactive with endometrial antigens, recurrent aborters had significantly lower proportions of asymmetric antibodies than healthy pregnant women [34].

Primarily murine experiments illustrate the presumed importance of PIBF for the maintenance of pregnancy. In one study, a neutralising anti-PIBF antibody was injected into one uterine horn on day 8 and a control antibody was injected into the other horn. After 2 days, all embryos had been aborted in the horn treated with the anti-PIBF antibody whereas all embryos had been retained normally in the control horn [30]. Another in vivo study in pregnant mice revealed similar results: the mice were randomly divided into three groups on day 8 of gestation, systemically treated with either the anti-PIBF antibody, RU-486 or placebo, and then sacrificed on day 10. In the first two groups, a significant loss of pregnancy as judged by the embryonic resorption rate, was observed compared with controls [30].

In another loss of pregnancy as judged by the embryonic resorption rate mice were sacrificed on day 10. In the first two groups, a significant increase in abortion rates was observed compared with controls [30].

Although dydrogesterone and other progesterone derivatives are frequently prescribed as luteal support for women with first-trimester bleeding, women having undergone assisted reproduction and women with a history of habitual abortions, there is still a marked need for more controlled, blinded and randomised clinical trials in order to draw firm conclusions as to the usefulness of dydrogesterone in women with a history of recurrent miscarriage. One such trial is currently ongoing at the University Hospital in Vienna. The trial began in summer 2003, proband recruitment is satisfactory at present and preliminary results are expected by the end of 2005.

5. Dydrogesterone in the treatment of habitual abortion

In one controlled, randomised but unblinded clinical trial, 114 women (aged 20–34 years) with a history of habitual abortions received either dydrogesterone (10 mg p.o. twice daily), human chorionic gonadotropin (hCG, 5000 IU i.m. once every 4 days) or no treatment until the 12th week of gestation. Treatment was started as soon as possible after confirmation of the pregnancy. Both dydrogesterone and hCG significantly reduced the abortion rate as compared with untreated controls (14% versus 16.5% versus 20%) with no increase in obstetric complications [40]. Likewise, in a similar trial including 146 women with first trimester vaginal bleeding and threatened abortion, treatment with 10 mg oral dydrogesterone twice daily significantly decreased the abortion rate as compared with untreated controls. Full-term delivery was achieved in 75.5% of women in the dydrogesterone group compared with 66.6% of the controls [40].

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6. Conclusion

The amount of evidence from published in vitro and in vivo studies in rodents, as well as in vitro and preclinical data in women, yield a promising view of a potent role for dydrogesterone in the management of threatened and recurrent abortion. Whether dydrogesterone repeatedly and reproducibly lowers abortion rates and therefore also con-
fers a practical, and not just a theoretical, advantage to these groups of women needs to be confirmed in reliable trials. As previously mentioned, one such trial is currently underway and will hopefully soon help to answer this question more precisely.

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