MHRA UK Public Assessment Report

Efficacy of progestogens in the maintenance of early pregnancy in women with threatened miscarriage or recurrent miscarriage

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EXECUTIVE SUMMARY

This Public Assessment Report reviews evidence for the efficacy of progesterone and dydrogesterone in the maintenance of pregnancy in women with threatened miscarriage or recurrent miscarriage. The safety of these treatments is also discussed briefly.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks.

For several decades, progesterone and progestogens (such as dydrogesterone) have been used to maintain early pregnancy. However, this practice seems to have been based on theoretical considerations rather than robust evidence of efficacy. Generally, the quality of much of the evidence is poor relative to today's standards. However, the methodological and ethical difficulties associated with conducting efficacy trials in these indications need to be considered.

Some degree of efficacy for progestogens in terms of successful pregnancy outcome has been demonstrated in the indication of recurrent miscarriage according to its strictest definition (ie, three previous consecutive unexplained spontaneous miscarriages). By contrast, in the indication of threatened miscarriage there is little to no convincing evidence of benefit from use of progestogens.

In view of the extensive worldwide use of progesterone and dydrogesterone, there does not seem to be any significant safety concerns either for the fetus or the mother associated with their use. However, difficulties associated with studying such a risk makes it possible that a very low level of risk has yet to be identified.

1. INTRODUCTION

Gestone, which contains progesterone, is authorised for use in women with recurrent miscarriage. Duphaston, which contains dydrogesterone (a synthetic form of progesterone), is also licensed for use in women with threatened miscarriage, but is being withdrawn from the market in March 2008 for commercial reasons.

Although both treatments have been used for many years to maintain early pregnancy, the evidence on which this practice is based is limited, and such progesterone supplementation is commonly done on an empirical basis. Moreover, knowledge about pregnancy has advanced substantially since many of the original studies were done, such that most are now outdated in terms of clinical practice and scientific rigour.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks. Here, the available evidence for the efficacy of progesterone and dydrogesterone in the maintenance of early pregnancy is reviewed.

2. PROGESTERONE IN PREGNANCY

2.1 Normal pregnancy

The hormone progesterone is needed to maintain pregnancy. At ovulation, the production of ovarian progesterone by a body called the corpus luteum rises sharply and peaks the following week. If the ovum is not fertilised, ovarian progesterone production falls, triggering endometrial shedding and menstruation. If the ovum is fertilised and it implants into the endometrial wall, the corpus luteum continues to secrete progesterone to prevent endometrial shedding, thereby protecting the developing fetus.

Later in pregnancy, the placenta takes over progesterone production—a switch that is regulated by the hormone human chorionic gonadotrophin (hCG). This switch was initially thought to occur at weeks 10–12 of gestation, but is now thought to occur earlier at weeks 6–7.

During the third trimester of pregnancy, levels of progesterone in the mother's bloodstream steadily increase, which, in addition to other factors, inhibits inappropriate uterine contractions.

2.2 Miscarriage of pregnancy

It is estimated that at least 60% of all natural conceptions do not result in a viable pregnancy, and that between 10% and 20% of all recognised pregnancies end in miscarriage.

The most common cause of miscarriage is the presence of a fetal chromosomal abnormality—in about 60% of miscarriages, a gross chromosomal abnormality is detectable in the expelled fetal material. Other risk factors include: maternal age older than 35 years; multiple pregnancies; structural uterine abnormalities; polycystic ovaries; autoimmune disorders; infections; poorly controlled diabetes; and environmental factors. However, many spontaneous miscarriages cannot be explained by any of these factors, and the role of progesterone in many aspects of early pregnancy has been investigated widely.

Threatened miscarriage is a relatively common random event that occurs during the first 20 weeks of gestation in about 20% of pregnancies. It is characterised by the occurrence of vaginal bleeding with or without abdominal cramps when the cervix is closed, but does not always result in miscarriage. It has been estimated that up to 85% of women who have had two previous miscarriages will conceive and carry normally afterwards.

Recurrent miscarriage is defined as three or more consecutive unexplained spontaneous miscarriages, and suggests an underlying problem rather than a random event. Recurrent miscarriage affects 1–2% of women.

Predictors for poor outcome of pregnancy are thought to include low levels of free serum hCG (ie, less than about 20 ng/mL) and low levels of serum progesterone (ie, less than about 14 ng/mL).

2.3 Progesterone in miscarriage

Historically, there was clear rationale for treatment of women with threatened or recurrent miscarriage with natural progesterone or synthetic progestogenic hormones (progestogens). In women with a threatened miscarriage, supplementary progesterone was thought to prevent the inappropriate onset of uterine smooth-muscle contraction due to low natural progesterone levels. In women with recurrent miscarriage, progestogen was given because the corpus luteum was not making enough to sustain pregnancy.

However, the clinical management and immunology of miscarriage has substantially advanced since most of the early work to support the use of progesterone in early pregnancy was done. The role of progesterone is likely to be far more complex than previously thought.

3. PHARMACOLOGY OF PROGESTOGENS

3.1 Progesterone

Progesterone is a hormone that is derived from cholesterol steroids and produced mainly by the corpus luteum and the placenta, with some contribution from the adrenal glands. It has a half-life of about 5 minutes and is metabolised mainly by the liver to pregnanediol. In the bloodstream, progesterone is bound mostly to albumin,

but about 20% is also bound to corticosteroid-binding globulin. When taken orally, progesterone is absorbed rapidly, but nearly all of a low dose is expected to be metabolised completely in one pass through the gut and liver. Therefore, progesterone-containing products are generally given non-orally.

3.2 Dydrogesterone

Dydrogesterone (6-dehydro-retroprogesterone) is a synthetic progestogen that was first made in the 1950s and is currently used widely worldwide. It is a potent orally active progestogen that has high affinity for progesterone receptors, low affinity for androgen receptors, and no affinity for oestrogenic receptors. It is claimed to be similar to natural progesterone both in its molecular structure and pharmacological effects. After administration, it is absorbed rapidly and achieves maximum blood plasma levels within 1-2 hours. Its primary metabolite, 20 α-dihydrodydrogesterone, is also a potent progestogen.

4. EFFICACY DATA

For several decades, progestogens have been used to maintain early pregnancy. However, this practice seems to have been based on theoretical considerations rather than robust evidence of efficacy. Studies to support efficacy in this indication span several decades and many are based on redundant clinical practice. Some studies do not include a comparator group, using instead theoretical estimates for the frequency of miscarriage in untreated women (now known to be over-estimates); many studies were done before it was possible to confirm by ultrasonography that pregnancy was viable. Furthermore, many studies included only a small number of women.

Although progestogens remain widely used worldwide to maintain early pregnancy, this practice may not be as common as it once was. In 1987, a UK survey indicated that about 13% of GPs recommended the use of progesterone to avoid threatened miscarriage, but that many did not believe this actually affected outcome.[1]

Although many studies have assessed the efficacy of progestogens as a class, every progestogen is diverse pharmacologically and thus the results from a study of one hormone cannot necessarily be extrapolated to others. Few studies have investigated specifically the use of progesterone or dydrogesterone in threatened miscarriage and recurrent miscarriage. These studies are reviewed below.

4.1 Threatened miscarriage

4.1.1 Progesterone

Gerhard I, et al. Biol Res Pregnancy Perinatol 1987; 8: 26-34[2]

In this double-blind, randomised, controlled trial, 26 women with bleeding in early pregnancy were allocated twice-daily progesterone vaginal suppositories, while 26 were allocated a polyethylene glycol vaginal suppository placebo. All women were prescribed bed rest. Women were further randomised according to the stage of gestation at which progesterone was given: 4-6 weeks; 7-10 weeks; or 11 weeks or later. In women with bleeding beyond week 7 of gestation (n=31), fetal heart action and movement was shown by sonography. Progesterone or placebo was given until the fetus was aborted or until 14 days after symptoms resolved.

Eight (15%) women had a miscarriage during the study. Women who bled before week 7 were at greater risk of miscarriage than those who bled after this time (30% *vs* 3%, respectively), as were those older than age 30 years compared with those who were younger (35% *vs* 6%, respectively).

The proportion of successful births in women who received progesterone (n=23, 89%) was not significantly different from those given placebo (n=21, 81%; table 1). Three miscarriages occurred in the progesterone group (12%) compared with five in the placebo group (19%).

Table 1: Effect of progesterone in patient subgroups

	Cases of miscarriage		
	Total	**Progesterone group (n=26)**	**Placebo group (n=26)**
All women (n=52)	8	3	5
Bleeding before 7 weeks (n=23)	7	3	4
Age older than 30 years (n=17)	6	1	5
History of miscarriage (n=29)	5	1	4

In the subset of women who bled before 7 weeks, progesterone treatment did not significantly decrease the frequency of miscarriage (table 1).

Despite elevated progesterone levels in the progesterone group, neither the intensity nor the duration of bleeding during treatment was significantly different from that of the placebo group.

Summary:

This small study found that progesterone did not significantly reduce the frequency of threatened miscarriage compared with placebo (12% *vs* 19%, respectively). In women who bled before 7 weeks of gestation, and who were therefore at the highest risk of miscarriage (accounting for 87% of all miscarriages), progesterone treatment had no significant effect on miscarriage frequency. However, the number of events in this trial was very small (eight miscarriages in total).

The researchers suggest that in other high-risk groups (including women who are older and women who have had previous miscarriages), the administration of progesterone may be beneficial relative to placebo. However, these analyses were not specified before the study started.

4.1.1.2 Dydrogesterone

Omar MH, et al. J Steroid Biochem Mol Biol 2005; 97: 421-25[3]

This prospective study recruited women with vaginal bleeding before 20 weeks' gestation to investigate the effectiveness of dydrogesterone in enabling women with threatened miscarriage to continue their pregnancy beyond 20 weeks' gestation. Women were excluded if they had a history of recurrent miscarriage, a missed miscarriage, evidence of tissue loss, presence of products of conception in the vagina, or an open cervix.

Of 194 women who were diagnosed as having threatened miscarriage at less than 13 weeks' gestation, 74 received dydrogesterone until bleeding stopped, together with bed rest and folic acid, and 80 women received bed rest and folic acid alone (ie, standard care). All women were followed up until 20 weeks' gestation; 21% dropped out during follow-up.

14 (9%) women had a miscarriage before 20 weeks of gestation—three in the dydrogesterone group and 11 in the standard-care group (table 2).

Table 2: Effect of dydrogesterone on prevention of threatened abortion

	Continuing pregnancy at week 20	Miscarriage before week 20
Dydrogesterone (n=74)	71 (96%)	3 (4%)
Control (n=80)	69 (86%)	11 (14%)

The difference between groups in the likelihood of continuing pregnancy beyond 20 weeks' gestation was of borderline significance (odds ratio for miscarriage 3·8 [95% CI 1·0–14·1], p=0·037). There was no statistically significant difference in miscarriage frequency according to presenting symptoms and ultrasonography findings.

Summary

In this study, it is not clear how women were assigned to a treatment group and therefore systematic bias may exist. Moreover, it is not clear whether treatment and control groups were stratified for the risk factors of threatened miscarriage. These factors; the small number of miscarriages; the very wide 95% CI; and uncertainty about from which treatment group the substantial proportion of women who dropped-out came means that it is not possible to draw any conclusions about the effect of dydrogesterone in women with threatened miscarriage from this study.

Kalinka J, Szekeres-Bartho J. Am J Reprod Immunol 2005; 53: 166-71[4]

This prospective study compared the levels of serum progesterone, serum oestradiol, and urine progesterone-induced blocking factor (PIBF[i]) in women with threatened abortion with those in women with normal pregnancy, and investigated the effect of dydrogesterone supplementation in the former group on the outcome of pregnancy.

43 women were between 6 weeks and 12 weeks of pregnancy. Of these, 27 showed clinical symptoms of threatened miscarriage (ie, bleeding, spotting, and uterine cramps) and were treated with dydrogesterone (30–40 mg/day for 10 days). 21 women had normal, healthy pregnancies and received no additional treatment. Blood samples were taken before treatment started and after 10 days. All women had detailed ultrasonography before treatment to assess gestational age of the fetus and to exclude multiple gestations or fetal abnormalities. Ultrasonography was repeated 10 days after treatment. All women were followed up until completion of pregnancy. No statistically significant differences in patient characteristics or gestational age existed between groups at baseline.

At first sampling, progesterone levels in women with threatened miscarriage did not differ significantly from those of women with a healthy pregnancy (24·3 ng/mL [±11·5] *vs* 22 ng/mL [±9·5]). 10 days after taking dydrogesterone, serum progesterone concentrations in women with threatened miscarriage had not increased (22·1 ng/mL [±10]) and were significantly lower than the levels in women with normal pregnancy (28·2 ng/mL [±9·6]).

Levels of urine PIBF were significantly lower in women with threatened miscarriage than in the control group before treatment (p=0·008). After dydrogesterone treatment, PIBF concentrations significantly increased (p=0·001), but to levels that were not different from those of the control group (p=0·26).

Pregnancy outcome in dydrogesterone-treated women was not significantly different from that of healthy controls: there were three ‘missed miscarriages’ (ie, no miscarriage has occurred, but the pregnancy is no longer developing) in the dydrogesterone-treatment group (11%) and one in the control group (6%). Gestation duration and birth weight of the babies were similar in the two groups.

[i] PIBF has been shown to prevent miscarriage in mice

Summary

This study found that the proportion of successful births in women with clinical symptoms of threatened miscarriage who were given dydrogesterone did not differ significantly from that in women with healthy pregnancies.

The incidence of miscarriage is thought to vary substantially, depending on the criteria used to define the population. In this study, the criteria for allocation to the dydrogesterone-treatment group were not specific and may have resulted in a low miscarriage frequency. The observed frequency in the treated group (11%) is similar to that of the untreated control group in Omar's study (14%).[3]

The use of healthy pregnancies as the comparator group is not appropriate because the actual number of miscarriages that would have occurred in the threatened-miscarriage group in the absence of treatment remains unknown, and the true size of any treatment effect cannot be measured. A complete lack of effect of dydrogesterone in this study cannot be excluded.

The small number of events (four miscarriages in total) questions the statistical significance of the findings. The only conclusion that can be drawn from this study is that oral dydrogesterone increases the level of a PIBF in the urine of pregnant women. Because the role of PIBF in human miscarriage remains unclear, the clinical importance of this observation is unknown.

4.2 Recurrent miscarriage

4.2.1.1 Progesterone

Swyer G, Daley D. Br Med J 1953; 1:1073-77[5]

113 women who had had at least two previous miscarriages before their 20th week of gestation were recruited from two hospitals. 53 women received no treatment and 60 women had six 25-mg progesterone pellets implanted in their gluteal muscles at no later than the 10th week of gestation or the time of the earliest previous abortion. Women were randomly assigned to progesterone treatment or no specific treatment in one hospital site, and were assigned on the basis of alternate cases in the other. Women with obvious complicating factors were excluded from the study.

Of the 60 women who received progesterone implants, 48 (80%) delivered live babies compared with 40 (75%) of those who received no treatment. However, this difference in outcome was not significant (p>0·7).

When women who had had three or more miscarriages were analysed separately (20 controls and 27 who received progesterone), the frequency of live births was higher in the progesterone-treated group (74%) than in the control group (55%). However, this difference was not statistically significant (p>0·2).

Summary

This was one of the first trials to compare the efficacy of progesterone with no treatment in recurrent miscarriage. Although women were randomly allocated to treatment, randomisation was crude and resulted in an imbalance between treatment groups for poor obstetric record (18% of women in the progesterone-treatment group had four or more previous miscarriages *vs* 9% of women in the control group).

Although no significant effect of progesterone was observed in the study population as a whole, this trial included women who had had only two consecutive miscarriages and did not fulfil the current definition of recurrent miscarriage (ie, three consecutive unexplained spontaneous miscarriages). Because women with fewer than three miscarriages accounted for 60% of the population, this study may have under-estimated any true effect of progesterone treatment.

When women with four or more miscarriages were included in a post hoc sub-group analysis, the rate of live births in the progesterone group (26% miscarriage frequency) was higher than that for untreated controls (45% miscarriage frequency).

These findings suggest that progesterone may have a role in the prevention of recurrent miscarriage.

4.2.1.2 Dydrogesterone

El-Zibdeh M. J Steroid Biochem Mol Biol 2005; 97: 431-34[6]

This prospective randomised, controlled trial investigated the effect of dydrogesterone, human chorionic gonadotrophin (hCG), or standard supportive therapy in women younger than age 35 years who had had at least three consecutive, unexplained, spontaneous miscarriages. Between 1994 and 2000, a wide range of medical assessments and detailed obstetric history was obtained from 500 women, whose partners were also examined for chromosomal and semen abnormalities. Of these, 180 women were found to have no alternative explanation for their recurrent miscarriage and were randomly assigned (according to the day of the week) to receive treatment with oral dydrogesterone (n=82), hCG (n=50), or no additional treatment (n=48) as soon as possible after confirmation of pregnancy. Most women continued treatment for 8 weeks, or until week 12 of gestation.

Fewer women who received dydrogesterone were admitted to hospital for vaginal bleeding during the treatment period compared with untreated controls (5% *vs* 10%, respectively), and significantly fewer experienced miscarriage (13% *vs* 29%, respectively, p=0·028; table 3). The frequency of miscarriage in the hCG group was slightly lower than in the dydrogesterone group, but was not significantly different from either the dydrogesterone group or the control group.

Table 3: Effect of dydrogesterone, hCG, or no additional treatment on pregnancy outcome

	Dydrogesterone (n=82)	hCG (n=50)	Control (n=48)
Miscarriage	11 (13%)*	9 (18%)	14 (29%)
Viable pregnancy	71 (87%)	41 (82%)	34 (71%)

*p=0·028 *vs* control

Summary

This study recorded a statistically significant reduction in miscarriage frequency in the dydrogesterone group compared with untreated controls.

Strengths of this study include the recruitment of women with a history of three or more consecutive spontaneous miscarriages and the exclusion of women who had an identifiable reason for miscarriage (other than luteal-phase defect). Furthermore, the inclusion of an untreated control group eliminates confounding by indication.

Weeks 6-7 of gestation are now considered to be critical for treatment of luteal-phase defect rather than weeks 10-12, on which many earlier studies were based. Most women in this study were treated as early as the 4th gestational week.

Limitations of the study include a lack of clarity about the study design, particularly the reason for the difference in treatment-group sizes and the quality of randomisation. For instance, differences in the type of problems experienced by women who attend clinics on different days of the week may result in bias. Of note, women in the dydrogesterone group were marginally older (42% *vs* 31% of women were older than age 30 years, respectively) and had had more previous miscarriages (36% with four miscarriages *vs* 29%, respectively).

4.3 Miscellaneous high-risk pregnancies

Oates-Whitehead RM. Progestogen for preventing miscarriage (review). Cochrane Database of Systemic Reviews 2003; 4: CD003511[7]

In 2003, the Cochrane Collaboration did a meta-analysis of all randomised controlled trials that assessed prophylactic progestogen supplementation on miscarriage frequency in various clinical settings.

Studies that were eligible for inclusion were randomised or quasi-randomised trials that compared prophylactic use of progestogens in the first 20 weeks of pregnancy for the prevention of miscarriage with placebo or no treatment. All doses, modes of administration, and treatment durations of natural progesterone and synthetic

progestogens were included in the meta-analysis. 14 studies of 1988 women fulfilled the inclusion criteria.

In five studies progestogens were given orally; in four studies they were given intramuscularly; in two studies oral and intramuscular progestogens were used together; in two studies progesterone was given via vaginal suppositories; and in one study progestogen pellets were inserted into gluteal muscle. The duration of treatment varied from 14 days to 36 weeks of gestation, or to miscarriage.

In one study patients were required to have had three or more consecutive miscarriages; in four studies women were required to have had two or more consecutive miscarriages; in seven studies women were accepted with threatened imminent miscarriage, irrespective of previous history; in one study women who had had amniocentesis were enrolled; and in the remaining study women who had undergone IVF (in-vitro fertilisation) were recruited. All studies included miscarriage as an outcome.

Seven studies accepted women within the first trimester of pregnancy; three accepted women to the 20th gestational week; and in the remaining four studies the gestational cut-off was unclear.

Meta-analysis of all studies showed no statistically significant difference in live-birth frequency between progestogen and placebo groups (odds ratio [OR] 1·05 [95% CI 0·83–1·34]).

No statistically significant difference in live-birth frequency compared with placebo was observed for progestogen given orally (OR 1·11 [95% CI 0·79–1·56]), intramuscularly (OR 0·77 [95% CI 0·36–1·68]), or vaginally (OR 0·74 [95% CI 0·40–1·35]).

The only significant reduction in miscarriage was associated with progestogen administration in women who had had three or more consecutive miscarriages immediately before the studied pregnancy (OR 0·39 [95% CI 0·17–0·91] compared with placebo or no treatment).

The authors suggest that there is no evidence to support the routine use of progestogen in the prevention of miscarriage in early to mid pregnancy, but that the trend towards improved live-birth frequency in women with a history of recurrent miscarriage deserves further study.

Summary

This meta-analysis of randomised controlled trials identified 14 trials published over 50 years that fulfilled the inclusion criteria. Individually, none of the 14 studies achieved significance for the efficacy of progestogen compared with placebo or no treatment. The quality of the studies, as judged by the authors, varied greatly.

Four studies accounted for 65% of the total weighting of the meta-analysis. Of these, two observed a trend in favour of placebo, one was neutral, and one observed a

trend in favour of progestogen. Such conflicting results may not be surprising in view of the various different progestogen products, control groups, routes and timing of progestogen administration, and the indications for treatment that were included in the meta-analysis.

No evidence was found for a role of progestogens in the maintenance of high-risk pregnancies. However, a sub-analysis of three studies of three different progestogens suggested that the administration of progestogens to women who had had at least three previous consecutive miscarriages (ie, recurrent miscarriage) immediately preceding the studied pregnancy significantly increased the chance of successful pregnancy. Individually, none of the studies showed a statistically significant effect for progestogen, but in all cases the trend was towards a reduced miscarriage frequency[ii].

4.3 Conclusions on efficacy

There is no good evidence that administration of progesterone or dydrogesterone effectively reduces the frequency of miscarriage in women with threatened miscarriage.

Compared with the standard of evidence that is required to support an application to market a new medicine, evidence for the efficacy of progestogens in recurrent miscarriage is extremely limited. However, the data suggest that progesterone and dydrogesterone may have a beneficial effect in women who have had three consecutive, unexplained, spontaneous miscarriages. Further work in this area is necessary.

5. SAFETY OF PROGESTOGENS

Globally, many women have received progesterone or progestogen treatment: dydrogesterone alone has an estimated worldwide exposure of more than 26 million women-years and more than 8 million fetuses.

Typical adverse effects of progesterone or progestogens for the mother include effects on bleeding pattern, nausea, breast changes, oedema, weight gain, mood swings, headache, insomnia, alopecia, hirsutism, transient dizziness, acne, allergic reactions, and rashes.

For the developing fetus, much observational data exist about the safety of progesterone or progestogens. However, many of these studies have important limitations: a lack of specific information on dose and timing of progestogen exposure (which may be critical for any effect on fetal organogenesis); sample sizes that in many cases are too small to detect a low level of risk; and poor control for potential

[ii] Swyer, 1953, progesterone OR 0·44 (95%CI 0·13-1·46); Goldzeiher, 1964, medroxyprogesterone OR 0·36 (0·04-2·99); Le Vine, 1964, hydroxyprogesterone OR 0·34 (0·08-1·44)

confounding factors—most importantly, confounding by indication. An abnormally developing fetus is likely to induce maternal bleeding and these women are therefore more likely to be treated with progestogens.

A careful study[8] in Japan that assessed the timing of hormonal exposure in relation to the precise congenital malformation in more than 700 aborted fetuses concluded that hormone therapy was not a cause of the apparent increase in frequency of abnormalities. In this study, the administration of hormones mostly occurred after the critical period of organogenesis. Moreover, hormones were more likely to be given to women who were carrying the most severely deformed fetus because these women bled more frequently in the first few weeks of pregnancy.

When an increase in the frequency of malformed children is observed in mothers who have been treated with hormones during early pregnancy to prevent miscarriage, the relation between the malformation, the treatment, and the indication for treatment becomes difficult, if not impossible, to disentangle.

Nevertheless, there is relatively little published evidence to support a harmful effect of progesterone or dydrogesterone in early pregnancy. The most common congenital abnormality that has been associated with progestogens is hypospadias, most recently in a study by Carmichael.[9] This retrospective case-control study found that the likelihood of cases of hypospadias having being exposed to progestogens was 3·7 times that of controls (95% CI 2·3–6·0).

However, this study[9] was not principally designed to investigate the effect of progestogens on the risk of hypospadias and therefore various essential data are lacking. For example, information on the use of progestogen—obtained from mothers up to 31 months after exposure—was not medically validated; information on dose, type, route, and frequency of administration of progestogen intake was not obtained; a substantial proportion of women did not provide the indication for their use of progestogens; the total number of exposed women was very small (42 cases and 31 controls); and 34% of the exposure to progestogens was as contraception—ie, only 48 women had taken progestogens for another purpose and confidence intervals are therefore wide.

Given the importance of timing of exposure to progestogens relative to both conception and the timing of fetal malformation, the date of conception is critical information. This information was provided by the mothers and was not medically validated.

If the critical gestational period for hypospadias is 8–14 weeks after conception and the observed association was causal, the risk would be expected to be highest in women given progestogen during this time. However, no discernable trend for the timing of progestogen use and the risk of hypospadias could be shown over different periconceptive and postconceptive periods.

No conclusions about the effect of progestogens in early pregnancy on the risk of hypospadias can be drawn from this study.[9]

Meta-analyses have been unable to confirm or refute an association between progestogens in pregnancy and an increased risk of fetal abnormality.

Few data are available for older children who were exposed in utero. A sudy[10] that followed for 30–40 years almost 4000 children who were exposed to progestogens during pregnancy found no significant difference in risk of hypospadias. Importantly, no cancers of the male genitalia, and no cases of clear-cell adenocarcinoma or cancer of the cervix uteri were identified. Furthermore, this study found no increase in the incidence of cancer in the mothers who were exposed to progestogens.

In view of the worldwide cumulative exposure of women to progestogens, there is little good evidence to suggest that the developing fetus or the mother is seriously harmed. However, the methodological difficulties of studying harm in these indications make it impossible to exclude the existence of a very low level of unidentified risk.

6. CONCLUSIONS

This Public Assessment Report reviews evidence for the efficacy of progesterone and dydrogesterone in the maintenance of pregnancy in women with threatened miscarriage or recurrent miscarriage.

In general, the quality of much of the evidence is poor compared with the standard that would be expected to support a new drug substance. However, the methodological and ethical difficulties associated with conducting efficacy trials in these indications need to be considered.

Some degree of efficacy in terms of successful pregnancy outcome has been shown in the indication of recurrent miscarriage, according to its strictest definition. Two randomised controlled studies[5,6] and a meta-analysis[7] provide limited evidence for a significant improvement in pregnancy outcome with progestogens. By contrast, in the indication of threatened miscarriage there is little to no convincing evidence of benefit for progestogens.

Assessment of the potential harm associated with exogenous progesterone or progestogens is made difficult by the presence of uncontrolled confounding by indication. However, given the extensive worldwide use of progesterone and dydrogesterone, there does not seem to be any significant safety concerns either for the exposed fetus or for the mother. However, it is possible that a very low level of risk has yet to be identified.

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8. GLOSSARY

Adrenal glands

Two glands located at the top of each kidney that perform important functions in the body

Affinity

The extent of attraction of one substance for another

Alopecia

Hair loss

Amniocentesis

Sampling of the fluid that bathes the fetus while in the womb in order to identify any abnormalities

Androgenic

Signalling in the body that leads to the development of male characteristics

Autoimmune disorders

An abnormality in which the body's immune system reacts against the tissues of the body

Clear-cell adenocarcinoma

A type of cancer

Confounding by indication

A type of bias that can occur in studies because participants with the worst prognosis are preferentially allocated to a particular treatment because of their disease state

Congenital malformation

An abnormality that is present at birth

Corpus luteum

A mass present in the ovaries that has an important secretory function

Double-blind, randomised, controlled trial

A study technique, regarded as robust, in which participants are enrolled onto the study and randomly assigned a treatment or treatment technique. In a **placebo** controlled trial, some patients are allocated the drug or technique of interest, whereas some are allocated **placebo** as a control group to identify the effects of the drug of interest. In a double-blind study, neither the trial participants nor the trial investigators are aware of who has been assigned to a particular treatment group, thus minimising bias

Endometrial

Relating to the lining of the womb

Fetal chromosomal abnormality

A defect in the genetic material (chromosome) of a fetus

Gestation

The time from fertilisation to birth

Gluteal muscles

The muscles of the buttocks

Hirsutism

Abnormal hairiness

Hypospadias

A birth defect that affects the uretra and genitals in males

Intramuscular

Administration of a drug directly into muscle

In utero

In the womb

In-vitro fertilisation

Fertilisation that takes place outside the body

Luteal-phase defect

An abnormality that affects the function of the **corpus luteum**

Meta-analysis

A study that combines the results from several similar clinical trials that asked the same study question and applies new statistical analysis

Immunology

The study of the immune system

Odds ratio

A measure of risk for one group compared with another (eg, risk for patients given progesterone compared with those given **placebo**). An odds ratio of more than 1 suggests an increased risk; an odds ratio of less than 1 suggests decreased risk. Odds ratios are usually accompanied by a 95% CI (confidence interval)—a statistical method of assessing the true difference between two groups: the range covered by this interval gives a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the odds ratio is regarded as statistically significant

Oedema

The accumulation of fluid in the tissues of the body

Oestradiol

A type of oestrogen hormone that is produced by the ovary

Organogenesis

The development of organs in a fetus

Ovulation

The release of an egg ready for fertilisation

Ovum

An egg: a female reproductive cell

Periconceptive

Relating to the time during conception

Pharmacological

Relating to the action of drugs in the body

Placebo

A dummy treatment

Polycystic ovaries

Enlargement of the ovaries that can lead to abnormalities such as abnormal menstruation

Postconceptive

Relating to the time after conception

Post hoc sub-group analysis

Investigation of a particular sub-group of participants in a study that was not planned at the beginning of the study

Prospective

A study in which people are recruited and subsequently followed over time

p value

A measure of the statistical probability of an event occurring by chance. Usually, a p value of less than 0·5 suggests the event is statistically significant and did not occur by chance, whereas a p value of more than 0·5 suggests the event is not statistically significant and arose by chance

Serum

The clear component of blood

Systematic bias

The tendency for a study to favour a particular outcome

Ultrasonography

A technique that uses sound waves to image parts of the body