Review Article

Evaluating the clinical efficacy and safety of progestogens in the management of threatened and recurrent miscarriage in early pregnancy- A review of the literature

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Abstract

Background Progestogens have been considered as a viable therapeutic option for the treatment of miscarriage for more than half a century.

Aim: The aim of the present review is to provide a comprehensive view of the literature regarding the clinical efficacy and safety effects of progestogens for preventing recurrent miscarriages and managing threatened miscarriage during early pregnancy.

Methods: A literature search was performed using electronic databases like Pubmed/ Medline to identify from 1953 to 2015. The search yielded around 27 original studies and review articles.

Results: Dydrogesterone (oral) and various micronized progesterone (MCP) given orally, vaginally and intramuscularly are the most commonly used progestogens for the treatment of recurrent and threatened miscarriages. Pharmacokinetic profile of dydrogesterone exhibits better bioavailability, receptor affinity, quick onset of action and a better half-life imparting long and stable effect. Dydrogesterone exhibits 47% and 29% statistically significant reduction in odds ratio of threatened and recurrent miscarriage when compared to standard of care. While, literature supports use of MCP (vaginal), recent findings suggest no statistically significant difference in live birth rate when compared to placebo (65.8% vs. 63.3%). MCP (vaginal) is associated with vaginal discharge and irritation whereas dydrogesterone (oral) avoids vaginal discharge and no birth defects have been associated with its use.

Conclusion: Treatment with dydrogesterone and other progestogens in general suggest dydrogesterone has number of advantages over other progestogens in terms of pharmacokinetic parameter clinical efficacy and safety profile. However, further studies are warranted to establish and promote the role of these progestogens in management of threatened and recurrent miscarriage.

Key Words: Progestogens, Recurrent miscarriage, Threatened miscarriage

Key Messages:

Bioavailability

- Oral bioavailability of dydrogesterone is approximately 5.6 times better than oral MCP.[32,37,82]
- Dydrogesterone is selective for progesterone receptor with 1.5 times better affinity than oral MCP.[32]
- Dydrogesterone exhibits quick onset of action reaching peak absorption levels within 30 minutes with a half-life of 5-7 hours imparting long and stable effect.[37]

Efficacy and safety

- Based on PROMISE study data vaginal MCP therapy did not significantly improve live birth rate in women with unexplained recurrent miscarriage compared to placebo.[57]
- Dydrogesterone leads to a 47% statistically significant reduction in the odds of a threatened miscarriage.[38]
- Dydrogesterone leads to 29% statistically significant reduction in the odds of a recurrent miscarriage.[39]
- Clinical experience with dydrogesterone does not provide evidence of a causal link between maternal dydrogesterone use during pregnancy and birth defects.[41]
- Use of medroxyprogesterone and hydroxyprogesterone in the management of miscarriages has not been supported in literature. They are indicated as contraceptive and for preventing preterm labor; respectively.[61,62,73]

Recommendations

- Dydrogesterone has been approved for pregnancy indication including threatened miscarriage, habitual miscarriage, and infertility.[81]
- Dydrogesterone has been recommended for the treatment of threatened and recurrent miscarriage by FOGSI and EPC guideline.[79,80]
- Oral MCP is not indicated for threatened and/or recurrent miscarriages.[81]

Introduction

Miscarriage is a common complication of pregnancy occurring in about 15%-20% of all clinically recognized pregnancies and results in spontaneous loss of pregnancy before 24 weeks' gestation.[1-3] Threatened miscarriage occurs often and forms a serious emotional burden for women. It is characterized by vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus with cardiac activity.[4] The

condition may progress to a miscarriage in approximately one-half of cases, or may resolve.[5,6] When bleeding is slight or resolves, pregnancy may continue normally but threatened miscarriage can be associated with a higher likelihood of adverse pregnancy outcome like prematurity (which is increased twofold), small-for-gestational-age babies (which is increased three-fold), and perinatal death.[7,8] In contrast, recurrent miscarriage, also known as recurrent pregnancy loss (RPL) or habitual abortion, is a distinct disorder defined by two or more consecutive spontaneous miscarriages.[9] It is estimated that fewer than 5% of women experience two consecutive miscarriages and only 1% will experience three or more.[10] The risk of recurrent spontaneous miscarriage is much higher in patients with previous losses and is estimated to be between 17% to 25% for women with two consecutive losses. The risk gets worse with increasing maternal age.[11,12] However, the pathophysiology of recurrent miscarriages is incompletely understood and despite investigation, no cause is found in more than 50% of the cases.[13-15] An array of etiologies exists in these patients making it a difficult condition to prevent and manage.[16-24] With limited understanding of the etiology, empiric treatment with varying degrees of success have been proposed to prevent this condition.[25-27]

Historically, low levels of circulating progesterone have been linked to impending miscarriage and the presence of associated vaginal bleeding.[28]Progestogen supplementation has been used as treatment for threatened miscarriage to prevent spontaneous pregnancy loss.[29,30] Progesterone is an essential hormone secreted by the corpus luteum that provides early pregnancy support until placental production takes over at 10 to 12 weeks of gestation. The term "progestogens" covers a group of molecules including both the natural female sex hormones progesterone and 17- hydroxyprogesterone (17 OH-PC) as well as several synthetic forms, all displaying the ability to bind progesterone receptors (PR).[31]Not all progestogens are equally suitable to be used as a replacement for endogenous progesterone as they differ not only with respect to their potency but also in their hormonal profile. Synthetic analogs of progesterone have been developed to improve oral availability and to produce longer lasting and more potent uterine effects than would be available from natural progesterone itself.[32] Depending upon the route of administration; progestogens manifest different biological effects that are due to differences in metabolism and binding affinities to the PR and other steroid receptors.[32]

Although progestogens have been investigated by many studies for more than half a century as therapeutic agents for the treatment of miscarriage, the poor methodological quality of these studies and the inclusion in the investigated population of women with undocumented fetal viability have resulted in

uncertainties associated with the use of this hormone and its effect on miscarriage.[33] The present paper aims to provide a comprehensive view of the literature on the clinical and safety effects of progestogens for preventing recurrent miscarriages and managing threatened miscarriage during early pregnancy. This review provides information on the progestogens that are most preferred in the treatment of threatened and recurrent miscarriages.

Methods

A literature search was performed using electronic databases such as Pubmed/Medline to identify relevant articles using relevant search terms for progestogens, threatened miscarriage, and recurrent miscarriages. From this search, publications that met the following criteria:-original contributions of progestogens with relevant product names, randomized control trials, observational studies, along with the review articles, systematic reviews and meta-analyses and reports limited to clinical human data that were published in the English language were included in the review. Case reports and case series were not included in the review. All articles considered were published in the scientific literature. Full text articles of relevant abstracts were assessed and evaluated. The search yielded around 32 original studies (randomized controlled, open and observational), systematic reviews and meta-analysis evaluating clinical efficacy and/or safety of progestogens in management of threatened and recurrent miscarriages which were reviewed and are included in the subsequent sections below.

Results
Brief overview of the clinical and safety profile of the most commonly prescribed progestogens
Dydrogesterone: Dydrogesterone, is a progestationally active retro-steroid,[34,35] is an orally active progestogen that is similar to endogenous progesterone in its molecular structure and has a high affinity PR.[36] Use of dydrogesterone is predicted to help establish an immune response, through inflammatory mediators like interleukins, in early pregnancy thereby preventing pregnancy loss. In contrast to numerous other synthetic progestogens, dydrogesterone has no androgenic side-effects in the mother (e.g. hirsutism, acne, etc.) Dydrogesterone also lacks estrogenic, anabolic and corticoid properties. It doesn't suppress the pituitary-gonadal axis at normal therapeutic doses and is therefore considered suitable for the management of women with pregnancy-related problems.[36] Dydrogesterone gains an advantage from its retro-structure and the presence of the C6–C7 double bond, which constricts the molecule into a rigid conformation suitable for binding with the PR. The greater rigidity of dydrogesterone also positively affects its selectivity, while natural progesterone is less selective, existing in

different conformations that more easily bind to different receptors.[37]

Findings from a recent meta-analysis including five controlled studies (RCTs) with 660 women who fulfilled the study criteria reported that there was a statistically significant reduction of 47% in the odds of miscarriage (CI=0.31-0.7) in women receiving dydrogesterone compared to those receiving standard of care.[38] Similarly, another meta-analysis including 509 women reported that there was a 29% reduction in the odds (CI=0.13-0.65) of a subsequent miscarriage in women receiving dydrogesterone compared to those receiving standard of care. Moreover, dydrogesterone is well tolerated and has no unwanted effects on the outcome of pregnancy.[39] Findings from a study among 133 women report higher pregnancy salvage rates in dydrogesterone group (92.0%) than in micronized progesterone (MCP) group (82.3%).[40](Table 1) A recent review assessing follow-up safety data on 1,380 patients suggest that the side effects including any birth defects are minimal, if any.[38,41](Table 2)

As per a recent retrospective case-control study, dydrogesterone is shown to be associated with congenital heart disease (CHD) during early pregnancy.[42] However; this study limits itself to the type and number of confounding information collected. A strong medical literature exists that suggests previous abortion as an important and strong risk factor for CHD in an offspring and no information on personal history of miscarriage was obtained in this particular study, making it a major methodological limitation of the study. The risk of residual confounding by indication, due to association of exposure and outcome with a personal history of abortion was very high in this study and thus the evidence of association of dydrogesterone with an increased risk of CHD derived from case-control study can be classified as minimum.[43] Evidence suggests that dydrogesterone has a number of advantages over MCP (oral and vaginal) in terms of pharmacokinetic parameters, safety, tolerability and convenience.[44]

Micronized Progesterone: MCP is available in natural or synthetic formulations for oral, intramuscular or vaginal administration in the form of suppository or gel. It is an exact duplicate of the progesterone produced in the corpus luteum and placenta therefore, is more readily metabolized by the body and is associated with minimal side effects.[45] Oral administration guarantees optimal compliance by patients however, 50-60% of dose is absorbed with only 6%-8% of absolute bioavailability which can be attributed to significant first-pass effect[46]; this route also results in side effects such as nausea, headache and sleepiness. The vaginal route results in higher concentrations in the uterus but does not reach high and constant blood levels. The drug administered intramuscularly occasionally induces non-septic abscesses, although it is the only route which

results in optimal blood levels.[47-51]Evidence suggests that vaginal progesterone can render higher endometrial availability than when administered intramuscularly. Vaginal administration enhances progesterone delivery to the uterus compared with a standard intramuscular regimen and results in a synchronous secretory endometrial histology.[52] Furthermore, findings from a study report the bioavailability of vaginal progesterone to be 4-8% (relative systemic).[53] However, in this study endometrial tissue concentration has been shown to be higher in vaginal progesterone (51.6 ng/mg) compared to intramuscular progesterone (0.71 ng/mg); with steady state of the concentration observed within 24-48 hours.[54]

Vaginal progesterone: There are relatively few studies (RCTs) evaluating the efficacy of vaginal progesterone in threatened and recurrent miscarriage. Findings from two RCTs conducted in a small group of patients (34 and 50 women), demonstrated statistically significant reduction in miscarriage risk of 0.33 (CI: 0.01- 7.65)[55] and 0.50 (CI: 0.17 - 1.45)[56] respectively, when compared with placebo. These findings should be approached with caution due to small sample sizes and wide confidence intervals. Furthermore, a recent large double-blind, placebo-controlled trial (PROMISE study) of vaginal MCP suppositories in 1,568 women reported no significant difference in the live birth rate with vaginal MCP (65.8%) as compared to placebo (63.3%). Thus, in women with first trimester of pregnancy, vaginal MCP is not seen to yield a significant higher live birth rate.[57](Table 1) There is no reported evidence of major side-effects associated with the treatment of vaginal progesterone, apart from headache and nausea.[54](Table 2)

Intramuscular and oral progesterone: Progesterone can be compounded for intramuscular administration, either as 17-hydroxy progesterone acetate or as caproate in a depot form, is suspended in oil for injection, and administered in doses at 50 mg per day. However, although intramuscular progesterone in oil generates high serum levels of progesterone, vaginal administration results in very high local progesterone concentration in endometrial tissue which is a preferred mode of progesterone administration.[58] Furthermore, there is slim to no data reporting the clinical efficacy and safety of intramuscular and oral progesterone use in prevention of threatened or recurrent miscarriage. The currently available literature supports their use in women to reduce preterm births and luteal phase support during infertility treatment.

17- Alpha hydroxyprogesteronecaproate: Hydroxyprogesterone (17 OH-PC) is a synthetic hormone and is approved for the treatment of preterm birth (birth of a baby at less than 37 weeks of gestation); however, it is also given for the treatment of

miscarriage. It binds with plasma protein like albumin and corticosteroid binding globulins. It has been shown by in vitro studies that 17 OH-PC can be metabolized by human hepatocytes. It is excreted in the urine and feces as a free steroid form and as conjugated metabolites.[59] However, the exact mechanism regarding how it prevents preterm birth is not clear.[60]

Furthermore, there is limited data available on the use of 17 OH-PC for the treatment of miscarriage and data that is available is very old, dating back to almost twenty years ago suggesting that17 OH-PC is not efficacious in preventing miscarriages.[61,62] No new literature is available that evaluates the use of 17 OH-PC in management of miscarriages. The available data for preterm birth suggests that 17 OH-PC prevents recurrent preterm births in approximately one third of the patient population but this would be overestimation of the benefit of the drug if we take into account the fact that only 15% preterm deliveries occur in women with prior preterm birth.[63] There is evidences that exogenous 17 OH-PC can cross the human placenta and is detectable in maternal and fetal blood for around 44 days of the last injection as it is slowly released from maternal fat. Some studies have suggested that 17 OH-PC might also be associated with increased risk of gestational diabetes[64,65] and there are isolated case reports on the development of transient parkinsonism[66] and autoimmune dermatitis.[67](Table 2)

Medroxyprogesterone acetate: Medroxyprogesterone acetate (MPA) a derivative of progesterone that has androgenic and anabolic effects and is administered either orally or intramuscularly.[68] It is primarily absorbed in the gastrointestinal tract and its maximum concentration is found between 2 to 4 hours of oral administration. Its bioavailability increases when taken with food. However, half-life of MPA does not change with food. Approximately 90% of MPA is protein bound, primarily to albumin. It is majorly metabolized in the liver by hydroxylation with subsequent conjugation and elimination in the urine. Most of the MPA metabolites are excreted in the urine in the form of glucuronide conjugates and minor amounts as sulfates.[69] The intramuscular (IM) administration shows a steady or slight increase in the plasma concentration while oral administration show a peak before 2 to 7 hours and subsequent decrease. The peak concentrations of MPA are 2-10 times higher in oral administration as compared to IM administration.[70]

Early studies on the use of medroxyprogesterone as an intervention for miscarriages have not reported any improvement in the risk of miscarriages.[71]It works by prevention of ovulation, and causes cervical mucus thickening, interfering with sperm injection[72] and causing changes to endometrium that are unfavorable for implantation.[73] Results of a subgroup analysis of a trial involving 223 women with recurrent miscarriages reported a statistically significant decrease in miscarriage rate with oral MPA compared to placebo or no treatment (odds ratio 0.38; 95%CI 0.20 to 0.70).[74](Table 1) However, the increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction reported with estrogen plus MPA prohibit its use.[75] (Table 2) As per The Royal Australian and New Zealand College of Obstetrician and Gynecologists Consensus-based recommendations, MPA is not recommended for pregnant women or those who have undiagnosed abnormal vaginal bleeding.[73] Moreover, USFDA has considered it to be a category X drug, which means that it is contraindicated in women who are or may become pregnant.[76]

Table 1: Clinical efficacy of progestogens

Study Citation	Study Design	Study Sample	Treatment arms	Clinical Efficacy Outcomes
For Threatened Miscarriage				
El-Zibdeh et al, 2009[44]	Randomized controlled study	146	Dydrogesterone vs. supportive care	Low miscarriage rate (17.5%) compared with supportive care alone (25%) (p<0.05)
Omar et al, 2005[87]	Prospective open study	154	Dydrogesterone vs. conservative treatment	Significantly higher (95.9%) continuing pregnancy success rate when compared with women receiving conservative treatment (86.3%); (p= 0.037)
Pandian et al, 2009[88]	Prospective, open, randomized study	191	Dydrogesterone vs. control	Statistically higher success rate (87.5%) in preventing miscarriages when compared with control group (71.6%) (p < 0.05)
Carp, 2012[38]	Meta-analysis	660	Dydrogesterone vs. standard of care	Reduction of 47% (CI= 0.31-0.7) in the odds for miscarriage, compared to standard of care and an absolute decrease in the miscarriage rate of 11%

Gerhard et al, 1987[55]	Randomized controlled study	34	Vaginal progesterone vs. placebo	Reduction in miscarriage risk ratio in comparison with the placebo (0.33)
Palagiano et al, 2004[56]	Randomized controlled study	50	Vaginal progesterone vs. placebo	Reduction in miscarriage risk ratio in comparison with the placebo (0.50)
Reijnders et al, 1988[61]	Double blind, Randomized study	64	17-alpha hydroxyprogesteronecaproate vs. placebo	Not advisable to prescribe during early pregnancy to prevent a miscarriage
Manganiello et al, 1981[62]	Observational study	7	17-alpha hydroxyprogesteronecaproate alone	Not advisable to prescribe during early pregnancy to prevent a miscarriage

Study Citation	**Study Design**	**Study Sample**	**Treatment arms**	**Clinical Efficacy Outcomes**
For Recurrent Miscarriage				
Ghosh et al, 2014[40]	Prospective, single-blinded, randomized comparative study	133	Dydrogesterone vs vaginal micronized progesterone	Higher pregnancy salvage rates in (92.0%) than in micronized progesterone (82.3%)
Carp, 2015[39]	Meta-analysis	509	Dydrogesterone vs. standard of care	Significant reduction of 29% (CI= 0.13-0.65) in the odds for miscarriage when compared to standard of care and an absolute reduction in the miscarriage rate of 12.5%
Kumar et al, 2014[89]	Double-blind, parallel, placebo-controlled study	360	Dydrogesterone vs. placebo	Statistically significant decrease in the number of miscarriages (6.9%) when compared with the placebo group (16.8%) (p=0.004) Statistically significant increase in the mean gestational age at delivery (38.0 2.0 weeks) in comparison with the placebo group (37.2 2.4 week) (p=0.002)
El-Zibdeh, 2005[34]	Randomized control study	180	Dydrogesterone vs. control	Abortions were significantly ($p \leq 0.05$) less common (13.4%) than in the control group (29%)
Coomarasamy et al, 2015[57]	Double blind, placebo-controlled randomized study	1,568	Micronized progesterone vs. placebo	No significant difference in the live birth rate of vaginal progesterone (65.8%; 95% CI, 0.94 to 1.15) when compared to placebo (63.3%; 95% CI, -4.0 to 9.0)
Hass et al, 2008[74]	Meta-analysis	223	Medroxyprogesterone acetate vs. placebo	Statistically significant decrease in miscarriage rate compared to placebo or no treatment (Peto odds ratio 0.38; 95% CI 0.20 to 0.70)

Table 2: Safety profile of progestogens

Study Citation	Study Design	Study Sample	Treatment arms	Clinical Safety Outcomes
Queisser-Luft, 2009[41]	Review	1,380	Dydrogesterone alone.	No evidence for congenital malformations associated with dydrogesterone use
Zainul Rashid et al, 2014[90]	Prospective cross-sectional comparative study	116	Dydrogesterone vs. control	Significantly lower (1.7%) incidence of gestational hypertension when compared to control group (12.9%) (p=0.001)
Simon et al, 1993[54]	Open labeled, randomized controlled study	58	Vaginal micronized progesterone alone	Headache and dymenorrhea each in 4 women and nausea in 3 women treated with vaginal progesterone
Tomic et al, 2015[91]	Double blind, randomized controlled study	831	Dydrogesterone vs. vaginal progesterone	Perineal irritation (p = 0.001), vaginal discharge (p = 0.001), vaginal bleeding (p = 0.04) and interference with coitus (p = 0.001) along with the total number of assessed side-effect (p = 0.001) with vaginal progesterone
Rode et al, 2011[92]	Randomized controlled study	334	Vaginal micronized progesterone vs. placebo	Reduction in increase in liver enzymes when compared to placebo (3.3% vs 7.3%, odds ratio:0.4)
Simon et al, 1993[54]	Open labeled, randomized controlled study	58	Intramuscular progesterone alone	The common adverse effect observed during intramuscular progesterone is headache (n=3)
Carmichael et al, 2005[93]	Case control study	73	Progesterone vs. control	3.7 times Hypospadias in case mothers compared to controls
Rebarber et al, 2007[64]	Prospectively collected database	2,081	17-alpha hydroxyprogesterone vs. control	17 OH-PC is associated with an increased risk of gestational diabetes (12.9% vs4.9%)
Water et al, 2009[65]	Retrospective cohort study	440	17-alpha hydroxyprogesterone vs. control	17 OH-PC is associated with an increased risk of gestational diabetes (10.9% vs3.6%)
Demirkiran et al, 2004[66]	Case report	1	17-alpha hydroxyprogesterone vs.	17 OH-PC is associated with transient parkinsonism
Bandino et al, 2011[67]	Case report	1	17-alpha hydroxyprogesterone alone	17 OH-PC is associated with autoimmune dermatitis
Resseguie et al, 1985[94]	Cohort study	988	17-alpha hydroxyprogesterone vs. progesterone	17 OH-PC is not associated with congenital anamolies
Yovich et al, 1988[95]	Unknown	1,016	Medroxyprogesterone acetate vs. control	No measurable teratogenic risk and certainly no risk for CHD and limb reduction defects

Discussion

Progestogens have been used as therapeutic agents to maintain early pregnancy and as a part of assisted reproductive technology.[77] Several guidelines have been developed to understand the use of progestogens for the treatment of threatened and recurrent miscarriage. As per The Royal Australian and New Zealand College of Obstetricians and Gynecologists Consensus-based recommendation, for women presenting with clinical diagnosis of threatened miscarriage evidence suggests

reduction in the rate of spontaneous miscarriage with the use of progestogens.[78] Similarly, the Position Statement on the Use of Progestogens by The Federation of Obstetric and Gynecological Societies of India (FOGSI) indicates beneficial evidence for the use of dydrogesterone.[79] The more recent European Progestin Club Guidelines (EPC) Consensus-based recommendation suggests that a reduction in miscarriage is observed with the use of dydrogesterone for women presenting with a clinical diagnosis of threatened and recurrent miscarriage.[80] Additionally, dydrogesterone is approved for pregnancy indication including all but not limited to menstrual disorders, threatened miscarriage, habitual miscarriage, infertility, endometriosis and in combination with hormonal replacement therapy. Oral MCP is indicated for endometrial hyperplasia in non-hysterectomized postmenopausal women but not for threatened and/or recurrent miscarriages.[81]

Dydrogesterone is structurally and pharmacologically similar to natural progesterone exhibits greater selectivity and binding affinity with PR avoiding other receptor related side effects. Consequently better bioavailability, reaching peak absorption levels within half an hour and progestational activity of main metabolite (20-, 21- and 16-hydroxy derivatives), is observed with lower dose of dydrogesterone (10-20 times) as compared to oral MCP. Furthermore, vaginal progesterone permits targeted drug delivery but for a shorter period of time.[32,37,38,82,83,84,85]

Based on a detailed review of literature with respect to the clinical efficacy, safety, and it is well established that dydrogesterone and vaginal MCP are the most commonly prescribed treatments for management of recurrent miscarriages. Though there is speculation regarding the role of progesterone in women with threatened miscarriage, recent evidence from well-designed robust studies suggests that the use of oral dydrogesterone during the first trimester of pregnancy has consistently lead to significant reductions in threatened and recurrent miscarriages as compared to other progestogens available in the market. Additionally, when used in comparison with vaginal progesterone, dydrogesterone was found to be as effective as the previous one. These findings provide a scientific basis for physicians to treat more women during their early pregnancy with oral dydrogesterone owing to its ease of use, high tolerability and fewer side-effects. Though evidence shows the use of vaginal MCP reduces the rate of miscarriages when compared with placebo[86] these studies are old and have been conducted in very small number of patients. Furthermore, it has been reported that the vaginal route is not well accepted by all patients due to side-effects such as vaginal irritation and discharge. Oral route is preferred by most of women as they find it more convenient.[40] In general, compared with the standard of

evidence that is required to support an application to market medicine, evidence for the efficacy of this progesterone in threatened and recurrent miscarriage is very limited.[33,55,56] Mainly, the findings are from a period when there were fewer diagnostic criteria available and the methodological rigor required (with respect to the process of randomization, treatment concealment, etc.) were less stringent than today.[33]

Assessment of the potential harm associated with exogenous progestogens (dydrogesterone and vaginal progesterone) 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. Typical adverse effects reported 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, little observational data exist about the safety of progestogens. However, it is important to keep in mind that many of these studies have important limitations which could include: 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 confounding factors—most importantly, confounding by indication. 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.

In conclusion, though there is data regarding the clinical efficacy and safety of oral dydrogesterone and vaginal MCP for treatment of threatened and recurrent miscarriage, further evaluation regarding the long term effects of these medicines on the fetus (benefits and side effects) are needed. Real-world studies with a large sample sizes and robust study design are warranted to establish and promote the role of these agents for the management of threatened and recurrent miscarriages during the first trimester of pregnancy in day to day clinical practice.

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Disclosure

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