RBMO

REVIEW

Dydrogesterone: pharmacological profile and mechanism of action as luteal phase support in assisted reproduction

BIOGRAPHY

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KEY MESSAGE

Dydrogesterone is a selective progesterone receptor agonist with high oral bioavailability. These key pharmacokinetic features allow for effective oral administration and may limit the risk of side-effects. Clinical studies have shown that oral dydrogesterone has a good benefit–risk profile, comparable to that of micronized vaginal progesterone, during luteal phase support.

ABSTRACT

The pharmacological and physiological profiles of progestogens used for luteal phase support during assisted reproductive technology are likely to be important in guiding clinical choice towards the most appropriate treatment option. Various micronized progesterone formulations with differing pharmacological profiles have been investigated for several purposes. Dydrogesterone, a stereoisomer of progesterone, is available in an oral form with high oral bioavailability; it has been used to treat a variety of conditions related to progesterone deficiency since the 1960s and has recently been approved for luteal phase support as part of an assisted reproductive technology treatment. The primary objective of this review is to critically analyse the clinical implications of the pharmacological and physiological properties of dydrogesterone for its uses in luteal phase support and in early pregnancy.

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INTRODUCTION

Progesterone is produced by the corpus luteum after ovulation and levels rise rapidly during the early- and mid-luteal phase of the menstrual cycle (*Csapo and Pulkkinen, 1978; Baird et al., 1997*), where it instigates secretory transformation of the endometrium, decidualization and uterine receptivity for implantation (*Bourgain et al., 1990; Segal and Casper, 1992; Kim et al., 2005*). Progesterone continues to be produced during pregnancy, where it is thought to be involved in preventing fetal rejection through immunomodulation and regulation of subendometrial blood flow (*Czajkowski et al., 2007; Arck and Hecher, 2013; Ghosh et al., 2014*). The importance of progesterone in the establishment and maintenance of pregnancy has been proven by interventional studies in early pregnancy, which showed that progesterone deficiency caused by a lutectomy or by blocking the actions of progesterone (using a progesterone antagonist) lead to pregnancy loss (*Csapo and Pulkkinen, 1978; Couzinet et al., 1986; Silvestre et al., 1990*).

Ovarian stimulation that is routinely used during IVF and assisted reproductive technology (IVF–ART) induces luteal phase deficiency, which can negatively affect implantation (*Macklon and Fauser, 2000; Beckers et al., 2003; Kolibianakis et al., 2003*). As a result, luteal phase support during IVF–ART is now considered standard practice to support implantation and to improve pregnancy rates (*Practice Committee of the American Society for Reproductive Medicine, 2008; van der Linden et al., 2015*). Luteal phase deficiency has also been purportedly linked to a number of clinical conditions, including infertility and pregnancy loss (*Swyer and Daley, 1953; Moszkowski et al., 1962; Blacker et al., 1997*); however, in these settings, luteal phase deficiency may be an epiphenomenon of other underlying disorders, such as polycystic ovary syndrome or anorexia (*Pirke et al., 1985; Filicori et al., 1991*).

Various progestogens have been investigated to support endogenous progesterone in the treatment of luteal phase deficiency. Only progesterone, dydrogesterone and 17α-hydroxyprogesterone caproate, however, are currently approved for clinical use during pregnancy (*Abbott BV, 2017; Bayer Schering Pharma AG, 2007; Besins Healthcare UK Ltd, 2017*). Dydrogesterone (6-dehydro-retroprogesterone) is a retroprogesterone, which was introduced for clinical use in an oral dosage form in the 1960s for the treatment of conditions associated with progesterone deficiency (*Backer, 1962*). Dydrogesterone is a selective progesterone receptor agonist, with better oral bioavailability compared with oral micronized progesterone (*Schindler et al., 2003; Rižner et al., 2011; Stanczyk et al., 2013*). For luteal phase support in the context of IVF treatment, a Cochrane review reported that oral dydrogesterone may be a more effective option than progesterone (*van der Linden et al., 2011*). This finding revived interest in the use of oral dydrogesterone for luteal phase support in this setting and prompted a large Phase III developmental programme (Lotus I and Lotus II studies), which led to the recent approval of oral dydrogesterone for luteal phase support in IVF–ART (*Abbott BV, 2017*). An increase in global oral dydrogesterone utilization for this purpose is, therefore, foreseeable, especially as patients prefer oral administration compared with injections or vaginal application (*Bingham, 1984; Arvidsson et al., 2005; Chakravarty et al., 2005*). This review, therefore, aims to summarize the pharmacological and physiological properties of dydrogesterone, by assembling widely available published evidence as well as addressing knowledge gaps and further research needs.

CLASSIFICATION OF PROGESTOGENS

Progestogens can be broadly classified into two groups: those that are structurally related to progesterone, which includes retroprogesterones such as dydrogesterone, along with 17-OH-progesterone derivatives and 19-progesterone derivatives; or those structurally related to testosterone, such as the 19-nortestosterone derivatives and the spironolactone derivative, drospirenone (*Druckmann, 2002; Stanczyk et al., 2013*) (FIGURE 1).

Depending on their structure, progestogens often have agonist or antagonist effects on androgen, glucocorticoid, oestrogen and mineralocorticoid receptors that can lead to side-effects (*Kuhl, 2005*). Because of cross-reactivity with other receptors (*Benagiano et al., 2009*), not all progestogens are suitable for use during pregnancy owing to the risk of potentially harmful effects to the developing fetus (*Kaňová and Bičíková, 2011*). For example, several 19-nortestosterone derivatives have been shown to have androgenic effects (*Schindler et al., 2003; Benagiano et al., 2009*) that may lead to masculinization of the female fetus (*Kaňová and Bičíková, 2011*). Exposure to progestogens that have potent glucocorticoid activity may alter fetal development by changing placental development and function (*Korgun et al., 2012*). Finally, exposure to progestogens that have potent oestrogenic or anti-androgenic activity may cause hypospadias in the developing fetus (*Wang and Baskin, 2008; Blaschko et al., 2012*). Progestogens that are approved for clinical use in pregnancy include progesterone, dydrogesterone and 17α-hydroxyprogesterone caproate (*Abbott BV, 2017; Bayer Schering Pharma AG, 2007; Besins Healthcare UK Ltd., 2017*) (FIGURE 1).

Progesterone has a steroidal structure with three cyclohexane rings and one cyclopentane ring; progestogenic activity is mediated through the 3-keto group and the double bond between carbons 4 and 5 (*Kuhl, 2005*). Dydrogesterone is a stereoisomer of progesterone with a methyl group at carbon 10 in the α-orientation rather than the β-orientation, and a hydrogen at carbon 9 in the β-orientation rather than the α-orientation (*Schindler et al., 2003; Colombo et al., 2006*). Dydrogesterone also has an additional double bond between carbons 6 and 7 (*Schindler et al., 2003; Colombo et al., 2006*). These unique molecular features create a 'bent' conformation with enhanced rigidity compared with progesterone, which is thought to account for dydrogesterone's high selectivity for progesterone receptors (*Schindler et al., 2003; Colombo et al., 2006*) (FIGURE 1).

Progesterone is manufactured for therapeutic use from the yam root (*Dioscorea* species) via Marker degradation (*Jasem et al., 2014*). Initially, the therapeutic use of manufactured progesterone was hampered by its poor bioavailability, but in the 1970s it was shown that decreasing the size

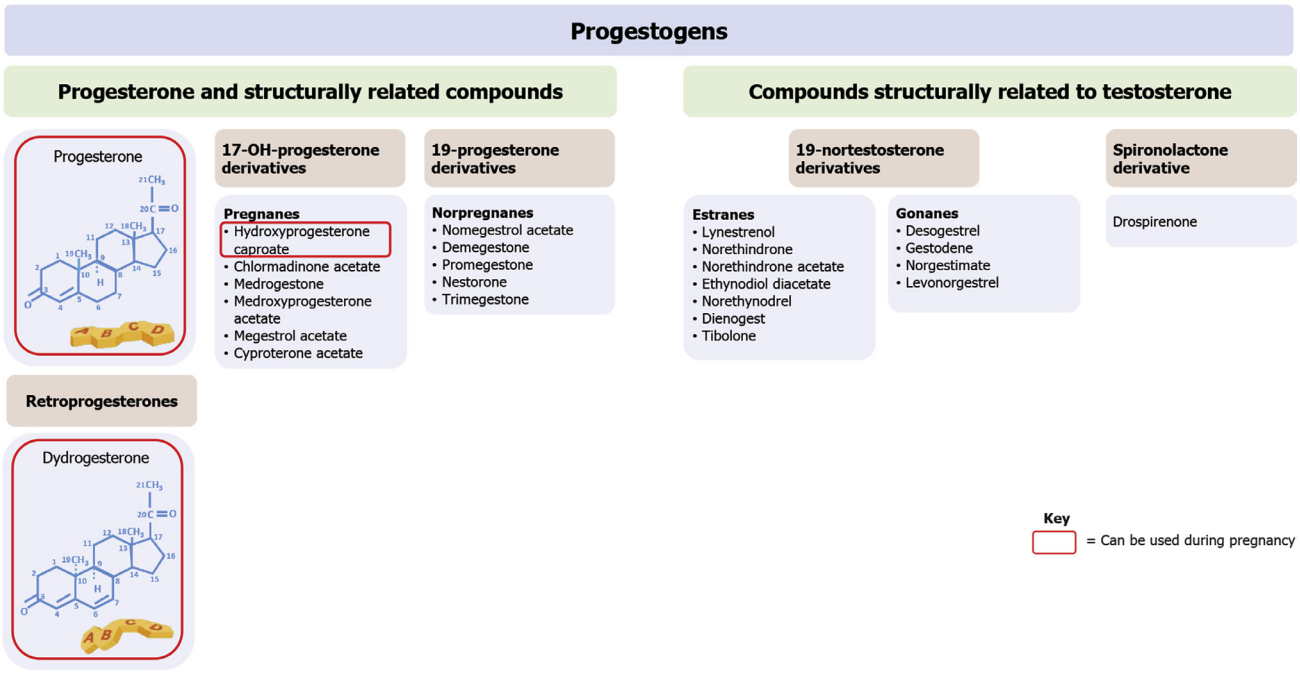

FIGURE 1 Classification of progestogens (*Druckmann, 2002; Stanczyk et al., 2013*), with the chemical structure of progesterone and dydrogesterone (*Schindler et al., 2003*). Progestogens can be classified into those structurally related to progesterone or testosterone. Progestogens that can be used during pregnancy are indicated and include progesterone, dydrogesterone, and hydroxyprogesterone caproate (*Abbott BV, 2017; Bayer Schering Pharma AG, 2007; Besins Healthcare UK Ltd, 2017*). Progesterone and all progestogens have a steroidal structure with three cyclohexane rings and one cyclopentane ring. Dydrogesterone has a methyl group at carbon 10 in the α-orientation rather than the β-orientation and a hydrogen at carbon 9 in the β-orientation rather than the α-orientation. Also, dydrogesterone has an additional double bond between carbons 6 and 7, which creates a 'bent' conformation, which is thought to mediate its key properties.

of progesterone particles through micronization could enhance its bioavailability (*de Lignières, 1999*). Progesterone can be formulated for oral, intravaginal, subcutaneous or intramuscular administration, with vaginal progesterone now the preferred route of administration for luteal support during IVF (*Vaisbuch et al., 2012; Sator et al., 2013*), despite administration-related side effects (*Tavaniotou et al., 2000*). Dydrogesterone, which is produced from progesterone (*European Patent Office, 1993*), is formulated for oral intake and has higher bioavailability than oral micronized progesterone (*Stanczyk et al., 2013*).

PHARMACOLOGICAL CHARACTERISTICS OF PROGESTERONE AND DYDROGESTERONE

Despite significant improvements in progesterone bioavailability through micronization (*de Lignières, 1999*), the systemic bioavailability of oral and vaginal micronized progesterone is still relatively poor, with values less than 5% and between 4% and 8%, respectively (*Stanczyk et al., 2013; Paulson et al., 2014*). In contrast, dydrogesterone has higher oral bioavailability (*Stanczyk et al., 2013*), which together with its activity and high specificity for progesterone receptors (*Rižner et al., 2011*), causes endometrial transformation at a dose 10–20 times lower than that of micronized progesterone (*King and Whitehead, 1986; Schindler et al., 2003*). The apparent efficacy of oral dydrogesterone at a relatively low dose may minimize side-effects (*Daughton and Ruhoy, 2013*) and reduce the likelihood of altered liver function (*Ghabril et al., 2010*). Overall, the extensive first-pass metabolism of oral progesterone limits its efficacy (*Paulson et al., 2014*) and high doses may increase the risk of intrahepatic cholestasis in predisposed women (*Bacq et al., 1997*). To circumvent these issues, the main routes of administration for luteal phase support during IVF to date have been intravaginal and intramuscular (*Paulson et al., 2014*), with subcutaneous progesterone introduced more recently (*Doblinger et al., 2016*).

In addition to bioavailability, receptor binding and activity are pivotal pharmacological features. Early endocrinological studies in animal models suggested that dydrogesterone had potent progestogenic activity, but no androgenic, glucocorticoid or oestrogenic activity (*Reerink et al., 1960; Aydar and Greenblatt, 1964; Vermorken et al., 1987*). More recent *in-vitro* receptor binding and transactivation analyses support these early findings (*Rižner et al., 2011*). Using a GeneBLAzer assay, *Rižner et al. (2011)* demonstrated that dydrogesterone had no or negligible agonistic activity at androgen, glucocorticoid and mineralocorticoid receptors (TABLE 1). In contrast, progesterone had relatively high agonistic activity at androgen receptors, but no or negligible agonist activity at glucocorticoid or mineralocorticoid receptors (*Rižner et al., 2011*).

Dydrogesterone also had relatively low antagonistic activity at glucocorticoid and mineralocorticoid receptors compared with progesterone (*Rižner et al., 2011*). Furthermore, although progesterone exerted anti-androgenic effects at the pre-receptor level with over 90% inhibition of 5α-reductase type 2 (an androgen-producing enzyme), dydrogesterone and 20α-dihydrodydrogesterone (DHD) showed only weak (up to 16%) inhibition

TABLE 1 RECEPTOR BINDING AFFINITIES AND ACTIVITIES OF DYDROGESTERONE VERSUS PROGESTERONE

Receptor	Parameter	Dydrogesterone	DHD	Progesterone
Progesterone receptor	RBA (%)	15.9	15.9	100
	Agonistic (RAA, %)	176	2	100
	Antagonistic (RIA, %)	<<	<<	<<
Androgen receptor	RBA, %	10.0	0.8	100
	Agonistic (RAA, %)	0.6	<<	100
	Antagonistic (RIA, %)	+[a,b]	+[a,b]	<<[b]
Glucocorticoid receptor	RBA, %	17.5	2.0	100
	Agonistic (RAA, %)	<<	<<	<<
	Antagonistic (RIA, %)	28	2	100
Mineralocorticoid receptor	RBA, %	NR	NR	NR
	Agonistic (RAA, %)	<<	<<	<<
	Antagonistic (RIA, %)	3	0.3	100
Oestrogen receptor-α	RBA, %	<<	<<	<<
	Agonistic (RAA, %)	NR	NR	NR
	Antagonistic (RIA, %)	NR	NR	NR

Data shown were taken from *Rižner et al. (2011)*; agonist and antagonist activity were analysed using a GeneBLAzer assay.

[a] RIA values were not calculated as the IC_{50} of the reference steroid progesterone was >10 000 nM.

[b] Progesterone exerted anti-androgenic effects at the pre-receptor level with over 90% inhibition of 5α-reductase type 2 (an androgen-producing enzyme), whereas dydrogesterone and its major metabolite showed only weak inhibition (up to 16%) of this enzyme.

<< specifies very low/negligible activity: values were not calculated if the EC_{50} or IC_{50} were >10 000 nM.

DHD, 20α-dihydrodydrogesterone; EC_{50}, half maximal effective concentration; IC_{50}, half maximal inhibitory concentration; NR, not reported; RAA, relative agonist activity; RBA, relative binding affinity; RIA, relative inhibitory activity.

of this enzyme (*Rižner et al., 2011*). Collectively, these data demonstrate that dydrogesterone, compared with progesterone, has high selectivity for progesterone receptors with low anti-androgenic effects at the pre-receptor level (*Rižner et al., 2011*), thus minimizing activation of other receptors and unwanted effects (TABLE 1).

Another pharmacological consideration is the quantification of progestogens after administration. Because of the structural differences with progesterone, neither dydrogesterone or DHD can be quantified by any commonly used diagnostic test for measuring progesterone levels. To specifically measure dydrogesterone or DHD levels, an instrumental chromatographic method needs to be used (*Abdel-Hamid et al., 2006*).

MECHANISMS OF PROGESTERONE ACTION

The progestogenic potency of various progestogens can be assessed by analysing morphological and biochemical changes to the endometrium after administration. *King and Whitehead (1986)* showed that, in patients with oestrogen-primed endometria, 6 days of treatment with oral dydrogesterone elicited biochemical changes consistent with secretory transformation at a dose of 10 mg, whereas oral micronized progesterone required a dose of 200 mg (*King and Whitehead, 1986*). In agreement with these data, biochemical analyses have shown that oral dydrogesterone doses of 10 mg and 20 mg for 12–14 days, in combination with oestrogen, were effective in inducing secretory transformation of the endometrium (*Siddle et al., 1990; Rees et al., 1991*).

More recently, *Fatemi et al. (2007)* analysed endometrial and endocrine profiles in six patients with premature ovarian failure treated with 20 mg oral dydrogesterone or 600 mg micronized vaginal progesterone. Using these non-equivalent doses, it was suggested that micronized vaginal progesterone was more efficient in creating an in-phase secretory endometrium compared with oral dydrogesterone (*Fatemi et al., 2007*). Reliably analysing endometrial changes by histology, however, is difficult and is, therefore, not necessarily an accurate measure of endometrial receptivity (*Duggan et al., 2001*).

In addition to inducing secretory transformation, many progestogens have high anti-gonadotrophic activity, which may affect ovulation (*Guerra et al., 2013*). During the menstrual cycle, the pituitary gland releases FSH and LH, which are involved in regulating the maturation of follicles and release of oocytes, respectively (*Holesh and Lord, 2017*). The anti-gonadotrophic actions of some progestogens suppress mid-cycle FSH and LH peaks, thereby inhibiting ovulation; as a result, these progestogens have been used in combined oral contraceptives together with oestrogen (*Guerra et al., 2013*).

Most of the available evidence indicates that dydrogesterone does not inhibit ovulation at the usual therapeutic doses. Several methods are accepted for analysing ovulation, including ultrasound, urinary steroid measurement, laparoscopy and basal body temperature (BBT) measurement (*Endrikat et al., 2011*). Early studies showed that oral dydrogesterone at doses between 10 mg and 40 mg did not affect the characteristic BBT pattern of the menstrual cycle and is, therefore, not hyperthermic (*Bishop et al., 1962; Bell and Loraine, 1965*). Similarly, oral dydrogesterone was shown to have no, or only a mild, effect on the pattern of urinary steroid excretion at doses

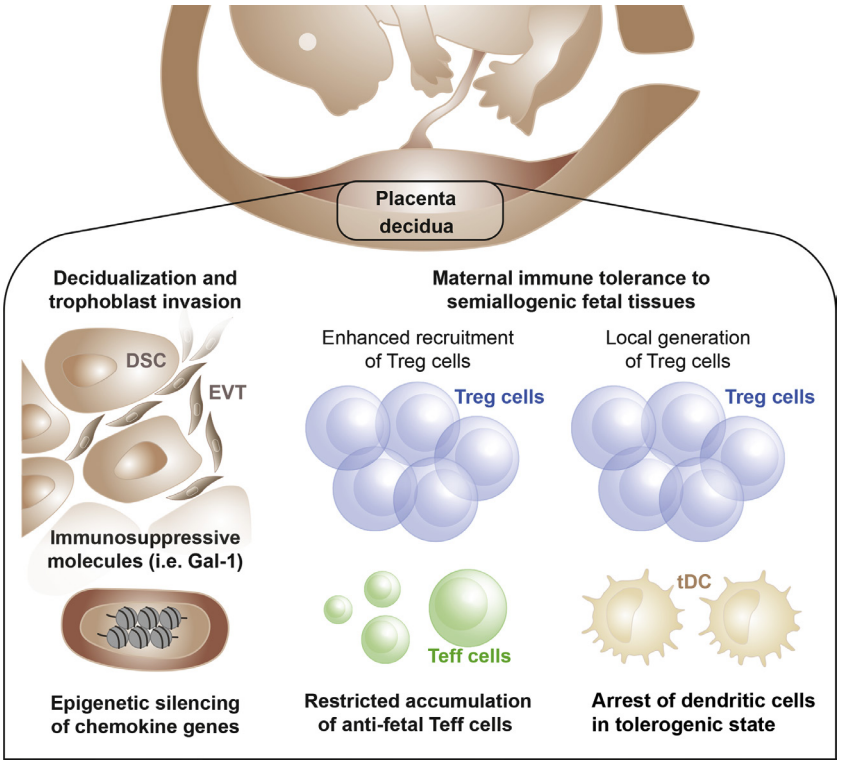

FIGURE 2 The potential immunomodulatory effects of progesterone[a]. Progesterone has multiple immunomodulatory effects, including expanding the number of local Treg cells (*Mao et al., 2010*), and arresting dendritic cells in a tolerogenic state (*Blois et al., 2007*). Progesterone increase the expression of the immunosuppressive molecule Galectin-1, which promotes the generation of tolerogenic dendritic cells (*Blois et al., 2007*). Progesterone may also epigenetically silence chemokine genes, thereby preventing homing of effector T cells to the decidua (*Nancy et al., 2012*). [a]The above immunomodulatory effects of progesterone have been investigated in murine models and remain to be proven in humans. DSC, decidual stromal cells; EVT, extravillous trophoblasts; Gal, galectin; tDC, tolerogenic dendritic cell; Teff, effector T cell; Th, T helper cell; Treg, regulatory T cell.

between 4 mg and 20 mg (*Swyer, 1964; Bell and Loraine, 1965; Larsson-Cohn et al., 1970*).

Despite the lack of effect of dydrogesterone on BBT and urinary steroid excretion patterns, its effect on mid-cycle LH surges is unclear. It has been shown that oral dydrogesterone at a dose of 4 mg does not affect LH surges (*Larsson-Cohn et al., 1970*); however, a dose of 20 mg was found to suppress LH surges (*Lenton, 1984*). More recently, the effect of oral dydrogesterone (20 mg) combined with human menopausal gonadotrophin on endocrine profiles during ovarian stimulation in IVF was evaluated versus oral micronized progesterone (100 mg) or medroxyprogesterone acetate (10 mg) combined with human menopausal gonadotrophin (*Zhu et al., 2017; Yu et al., 2018*). Oral dydrogesterone was similarly effective as oral micronized progesterone and medroxyprogesterone acetate in the prevention of premature LH surges (*Zhu et al., 2017; Yu et al., 2018*). These results, however, need to be taken in context as LH surges are not a definite marker of ovulation (*Zalányi, 2001*), and the supraphysiological oestradiol levels during ovarian stimulation may modulate the sensitivity of the pituitary gland (*Wang and Yen, 1975*). Finally, the most definitive evidence that dydrogesterone does not inhibit ovulation comes from small clinical studies investigating the use of oral dydrogesterone to treat endometriosis-associated infertility, in which a substantial proportion of patients became pregnant while undergoing oral dydrogesterone therapy (*Tumasian et al., 2001; Makhmudova et al., 2003*).

Progestogens can also modulate immune responses; this is of importance in the context of pregnancy, as the embryo expresses antigens foreign to the maternal immune system (*Mincheva-Nilsson, 2003*). The immunomodulatory mechanisms regulating maternal tolerance to such semi-allogeneic fetal tissue have increasingly been shown to be complex; however, progesterone is thought to play a key role in mediating such immune tolerance (*Szekeres-Bartho et al., 2001*). Initially, it was suggested that progesterone prevents fetal rejection by favouring a T helper cell 2 (Th2) inflammatory response over a T helper cell 1 (Th1) response, e.g. via the synthesis of progesterone-induced blocking factor (PIBF) (*Szekeres-Bartho et al., 2001*).

It is now known that the Th1/Th2 paradigm is too simplistic and maternal–fetal tolerance involves complex interplay between a variety of immune cells and signalling molecules (*Arck and Hecher, 2013*) (FIGURE 2). Regulatory T (Treg) cells have been shown to have an important role in maternal–fetal immune tolerance (*Mao et al., 2010*). In mice, progesterone expands the number of systemic and local uterine Treg cells during mid-term pregnancy and enhances their immunosuppressive functions (*Mao et al., 2010*). The mechanism by which progesterone exerts its effects on Treg cells, however, remains to be determined. *Engler et al. (2017)* suggested that progesterone expands the numbers of Treg cells by promiscuous binding to glucocorticoid receptors on T cells.

Areia et al. (2015) found that about 8% of Treg cells in pregnant women express the membrane progesterone receptor-α (mPRα). As nuclear progesterone receptors (PR-A and PR-B) have not been consistently identified in human T cells (Dosiou et al., 2008), activation of mPRα could be important in mediating the immunomodulatory functions of progesterone (Areia et al., 2015).

Dendritic cells are also key in regulating maternal–fetal tolerance as demonstrated in murine models. Pre-implantation, depletion of dendritic cells is associated with implantation failure (Krey et al., 2008). After implantation, dendritic cells are arrested in a tolerogenic state in successful pregnancies; these cells are expanded, recruited, or both, by the decidual expression of Galectin-1 and promote the expansion of Treg cells and Th2 immune responses (Blois et al., 2007). Dydrogesterone has been shown to up-regulate Galectin-1 expression in mice, whereas Galectin-1 up-regulates PIBF expression, indicating that Galectin-1 is linked with the progesterone-PIBF axis (Blois et al., 2007). Collectively, these data suggest that systemic progestogens could be important in tailoring the maternal immune adaption towards the promotion of fetal tolerance; however, some of the immunomodulatory effects are yet to be investigated in humans and the clinical implications, therefore, remain speculative.

Appropriate immunomodulatory signals are key for maintaining pregnancy; however, subendometrial blood flow may also play a role by providing an adequate oxygen and nutrient supply to the developing embryo (Czajkowski et al., 2007). This has been supported by evidence that elevated uterine arterial resistance and reduced blood flow is associated with recurrent pregnancy loss (Abdel-Razik et al., 2014). Both micronized vaginal progesterone and oral dydrogesterone have been shown to lower the uterine arterial systolic–diastolic ratio and vascular resistance in women with threatened or recurrent miscarriage, suggesting improved endometrial blood flow (Czajkowski et al., 2007; Ghosh et al., 2014). Nitric oxide plays a role in increasing uterine blood flow during the luteal phase and in early pregnancy (Abdel-Razik et al., 2014), and progesterone has been shown to increase nitric oxide synthesis in human vascular endothelial cells *in vitro*, mainly mediated through mPRα (Pang et al., 2015). Although dydrogesterone itself has a minimal effect on nitric oxide synthesis in human vascular endothelial cells, its main metabolite DHD elicits a consistent increase in nitric oxide synthesis from these cells (Simoncini et al., 2006). The clinical implications of these effects of progesterone and dydrogesterone in early pregnancy or luteal phase support, however, remain to be determined.

LUTEAL PHASE SUPPORT IN IVF AND ASSISTED REPRODUCTIVE TECHNOLOGY

Ovarian stimulation during IVF–ART involves the use of gonadotrophin-releasing hormone (GnRH) analogues (both agonists and antagonists), which prevent premature luteinization and ovulation (Practice Committee of the American Society for Reproductive Medicine, 2008). Although it is well established that ovarian stimulation can lead to a defective luteal phase, the mechanisms behind this effect have been debated for many years. It is thought that supraphysiological levels of steroids secreted during the follicular phase or early luteal phase after ovarian stimulation may inhibit LH secretion from the pituitary gland (Edwards et al., 1980; Sungurtekin and Jansen, 1995; Fauser and Devroey, 2003; Fatemi, 2009). This may result in a lack of support for the corpus luteum, thereby shortening the luteal phase and causing luteolysis (Duffy et al., 1999; Beckers et al., 2003; Fauser and Devroey, 2003). As a result, luteal phase support using progestogens has been recommended when GnRH analogues are used during IVF–ART (Practice Committee of the American Society for Reproductive Medicine, 2008). These recommendations are supported by a recent systematic review that demonstrated that luteal phase support with progesterone was associated with higher live birth and pregnancy rates compared with placebo or no treatment (van der Linden et al., 2015).

Oral micronized progesterone is not commonly used for luteal phase support as there is some evidence that it may not be as effective as vaginal or intramuscular formulations, although this has not been proven (Friedler et al., 1999; Licciardi et al., 1999; Paulson et al., 2014; van der Linden et al., 2015). Although no single progesterone formulation or regimen has been identified as superior in efficacy (van der Linden et al., 2015), the vaginal route is generally preferred at IVF–ART centres as it avoids injection-site pain and the abscesses associated with progesterone injections (Tavaniotou et al., 2000; Vaisbuch et al., 2012; Beltsos et al., 2014). Vaginally administered progesterone, however, is associated with its own administration-related side-effects, such as interference with coitus, vaginal bleeding, irritation and discharge (Lockwood et al., 2014; Tomic et al., 2015). Micronized vaginal progesterone for luteal phase support can be administered either as suppositories, tablets, or as an 8% gel (Practice Committee of the American Society for Reproductive Medicine, 2008).

Dydrogesterone is an alternative to progesterone for luteal phase support in IVF–ART. Numerous small-scale clinical studies and a meta-analysis have indicated that oral dydrogesterone is at least as efficacious as micronized vaginal progesterone in supporting pregnancy rates after luteal phase support (Chakravarty et al., 2005; Patki and Pawar, 2007; Ganesh et al., 2011; Salehpour et al., 2013; Tomic et al., 2015; Barbosa et al., 2016; Saharkhiz et al., 2016; Zargar et al., 2016). More recently, the randomized, double-blind, double-dummy, Phase III Lotus I clinical study, conducted in 1031 patients, compared oral dydrogesterone (30 mg [10 mg three times daily]) with micronized vaginal progesterone capsules (600 mg [200 mg three times daily) for luteal phase support in fresh cycle IVF (Tournaye et al., 2017). In this double-blind, double-dummy study, non-inferiority of oral dydrogesterone to micronized vaginal progesterone capsules was demonstrated, with pregnancy rates at 12 weeks of gestation in the full analysis set of 37.6% and 33.1% in the oral dydrogesterone and micronized vaginal progesterone capsule treatment groups, respectively (Tournaye et al., 2017). The second study in the Phase III Lotus clinical trial program (Lotus II), although being an open-label, randomized study, followed a similar overall design to Lotus I, and compared oral dydrogesterone (30 mg [10 mg three times daily]) with 8% micronized vaginal progesterone gel (90 mg once daily) (Griesinger et al., 2018). Lotus II demonstrated non-inferiority of oral dydrogesterone to micronized vaginal progesterone gel for luteal phase support

in fresh cycle IVF, with pregnancy rates at 12 weeks gestation in the full analysis set of 38.7% and 35.0% in the oral dydrogesterone and micronized vaginal progesterone gel treatment groups, respectively (*Griesinger et al., 2018*).

The results of a prospective, randomized, comparative study demonstrated that the percentage of patients satisfied with the tolerability of treatment was significantly higher in the oral dydrogesterone group versus the micronized vaginal progesterone group (*Chakravarty et al., 2005*). No patients in the oral dydrogesterone group experienced vaginal pain or irritation, but these administration-related side-effects were reported in 10.5% of patients in the micronized vaginal progesterone group (*Chakravarty et al., 2005*). Moreover, another randomized clinical study demonstrated that perineal irritation, vaginal bleeding, vaginal discharge and interference with coitus were significantly lower in the oral dydrogesterone group compared with the micronized vaginal progesterone gel group (*Tomic et al., 2015*). These data are supported by studies that compared oral versus vaginal formulations of non-progestogen drugs, which showed that women preferred to use oral formulations compared with vaginal ones (*Bingham, 1984; Arvidsson et al., 2005*).

The efficacy of oral dydrogesterone for luteal phase support in fresh cycle IVF is well established (*Chakravarty et al., 2005*; *Patki and Pawar, 2007*; *Ganesh et al., 2011; Salehpour et al., 2013; Tomic et al., 2015; Barbosa et al., 2016*; *Saharkhiz et al., 2016; Zargar et al., 2016; Tournaye et al., 2017*); however, limited data are available about its use in artificial frozen-thawed cycles, which have different underlying endocrinological issues. The lack of ovulation in artificial frozen-thawed cycles causes an absence of endogenous corpora lutea, meaning that the endometrial changes necessary for implantation and early pregnancy are totally dependent on exogenous progestogen supplementation (*Ghobara et al., 2017*). The use of oral dydrogesterone in artificial frozen-thawed cycles has been investigated in two small randomized clinical studies (*Rashidi et al., 2016; Zarei et al., 2017*). *Rashidi et al. (2016)* reported comparable pregnancy rates between the oral dydrogesterone and micronized vaginal progesterone groups, using equivalent doses of 40 mg and 800 mg, respectively (*Rashidi et al., 2016*) Conversely, *Zarei et al. (2017)* reported a lower pregnancy rate in the oral dydrogesterone group compared with the micronized vaginal progesterone group, using non-equivalent doses of 20 mg and 800 mg, respectively. Overall, further studies are needed to investigate the efficacy and optimal dosing schedule of oral dydrogesterone during artificial frozen-thawed cycle IVF.

SAFETY DATA RELATED TO PROGESTOGEN USE

It is estimated that 113 million women and about 20 million fetuses have been exposed to dydrogesterone since 1960 (*Tournaye et al., 2017*). Overall, clinical studies have demonstrated that oral dydrogesterone has a good benefit–risk profile comparable to that of micronized vaginal progesterone during luteal phase support (*Chakravarty et al., 2005; Tomic et al., 2015; Tournaye et al., 2017*). In maternal populations, liver function analyses (*Chakravarty et al., 2005; Tournaye et al., 2017*), as well as the incidence of vascular, gastrointestinal and nervous system disorders (*Tournaye et al., 2017*), were comparable between the oral dydrogesterone and micronized vaginal progesterone capsule groups. Furthermore, the Lotus I study demonstrated that the incidence of maternal serious treatment emergent adverse events was similar between the oral dydrogesterone and micronized vaginal progesterone capsule groups, occurring in 10.8% and 13.3% of participants, respectively (*Tournaye et al., 2017*). In the newborn population, the incidence of serious adverse events was low, occurring in 4.2% and 5.7% of participants in the oral dydrogesterone and micronized vaginal progesterone capsule groups, respectively (*Tournaye et al., 2017*). Overall, newborn safety data, including the incidence of congenital, familiar and genetic disorders, were comparable between the oral dydrogesterone and micronized vaginal progesterone capsule groups in the Lotus I study (*Tournaye et al., 2017*).

In the Lotus II study, the incidence of maternal serious treatment emergent adverse events was similar between the oral dydrogesterone and micronized vaginal progesterone gel groups, occurring in 13.7% and 13.1% of participants, respectively (*Griesinger et al., 2018*). Furthermore, in the fetal and newborn population, the incidence of serious treatment emergent adverse events was comparable between the oral dydrogesterone and micronized vaginal progesterone gel groups, occurring in 12.7% and 11.4% of participants, respectively; the incidence of congenital, familial and genetic disorders were also similar between the oral dydrogesterone and micronized vaginal progesterone gel groups (*Griesinger et al., 2018*).

A recent retrospective case-controlled study in 202 children that investigated the use of oral dydrogesterone in early pregnancy to prevent miscarriage reported a positive association between congenital heart malformations and oral dydrogesterone treatment (*Zaqout et al., 2015*). However, this study did not implement three key principles in their study design to reduce selection, confounding and information bias. To reduce selection bias, the groups should have only included offspring whose mother had experienced miscarriage, as oral dydrogesterone is indicated in early pregnancy for the treatment or prevention of miscarriage as well as, more recently, luteal support in ART–IVF (*Abbott BV, 2017*). There is strong evidence that previous miscarriages are an important risk factor for congenital heart defects (*Tikkanen and Heinonen, 1992; Liu et al., 2009; Shi et al., 2015*); as such, confounding bias could have been avoided by choosing offspring whose mother had experienced miscarriages as a study base. Finally, they did not confirm oral dydrogesterone exposure in medical records, but relied on the mother's recollection of oral dydrogesterone usage, which is no guarantee of comparable drug exposure. As a result of these weaknesses in the study design, no association of a causal relationship can be concluded.

In the Lotus II study, the of incidence congenital heart malformations was low, occurring in six cases and 10 cases of fetuses and newborns in the oral dydrogesterone and micronized vaginal progesterone gel groups, respectively (*Griesinger et al., 2018*). The Lotus I study reported three congenital heart disease events in each treatment group (*Tournaye et al., 2017*).

Of note, the 2017 European Society of Human Reproduction and Embryology guidelines for the prevention of recurrent pregnancy loss (miscarriage) state that vaginal progesterone use during early

pregnancy has no beneficial effect in women with unexplained recurrent pregnancy loss. There is some evidence that oral dydrogesterone treatment, initiated when fetal heart action can be confirmed, may be effective but more trials are needed (*ESHRE Early Pregnancy Guideline Development Group, 2017*).

Overall, oral dydrogesterone has a well-established safety profile; the results of the large and robust Lotus I and Lotus II Phase III clinical trials revealed no new safety concerns related to oral dydrogesterone use during early pregnancy for either the mother or the developing fetus, and no increased risk of congenital heart disease has been identified (*Mirza et al., 2016; Tournaye et al., 2017; Griesinger et al., 2018*).

CONCLUSIONS

Overall, dydrogesterone has a favourable pharmacological profile. Dydrogesterone is a selective progesterone agonist, allowing specific progestogenic effects in relevant cell types. As shown in clinical studies, the benefits of oral dydrogesterone treatment in luteal support outweigh the risks if it is used as recommended.

The pharmacological profile of dydrogesterone enhances its progestogenic effects versus progesterone, indicated by the fact that an equivalent dose of oral dydrogesterone is 10–20-fold lower than that of oral micronized progesterone (*Schindler et al., 2003*). Although an equivalent dose versus micronized vaginal progesterone remains to be accurately determined, the Lotus I study demonstrated that a 20-fold lower dose of oral dydrogesterone (30 mg) is non-inferior to micronized vaginal progesterone (600 mg) for luteal phase support (*Tournaye et al., 2017*). Although the implications of some of the immunomodulatory features of progesterone remain to be proven in the clinical setting, it is likely that dydrogesterone mimics the effects of progesterone through binding to progesterone receptors. It will be interesting to determine whether oral dydrogesterone is a more effective systemic immunomodulator than vaginal progesterone owing to its administration route; further studies are required in this area.

The unique structure of dydrogesterone results in enhanced oral bioavailability versus progesterone, allowing for effective oral administration and circumventing the inconvenience and discomfort related to intravaginal or intramuscular progesterone applications. The Lotus I and Lotus II Phase III studies demonstrated that oral dydrogesterone is a well-tolerated and efficacious treatment during luteal phase support; as a result, oral dydrogesterone may replace micronized vaginal progesterone as the standard of care owing to its patient-friendly oral administration route (*Tournaye et al., 2017; Griesinger et al., 2018*). Oral dydrogesterone may induce a paradigm shift in the treatment of the estimated 1.5 million women worldwide undergoing IVF each year (*Chambers et al., 2012; Tournaye et al., 2017*).

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