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IF IT'S ORALLY EFFECTIVE IT'S

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Dydrogesterone Tablets IP 10mg

EXPOSURE IN OVER **94** MILLION PATIENT**

EXPERIENCE OF MORE THAN **55** YEARS OF USAGE##

EXPOSURE IN OVER **20** MILLION PREGNANCIES** ^

REACH OF MORE THAN **100** COUNTRIES GLOBALLY‡

CONTENTS

An insight into the unique properties, efficacy and safety of dydrogesterone

An insight into the unique properties, efficacy and safety of dydrogesterone

OVERVIEW

- Dydrogesterone is a potent orally-active synthetic progestin that is widely utilized in the clinical setting since a long time.[1] The compound belongs to a class of progestins called retroprogesterone (Table 1)[2]
- It is a stereoisomeric form of progesterone and it appears to be a highly selective progestin which, due to its retrostructure, binds almost exclusively to the progesterone receptor.[3]

MECHANISM OF ACTION

- Dydrogesterone is considered to act on progesterone receptors in the uterus and promote healthy growth and normal shedding of the endometrial lining[4]
- The compound does not exhibit any estrogenic, androgenic or anti-androgenic effect. Additionally, it is regarded to be non-thermogenetic and non-sedative[5] It neither inhibits nor interferes with gonadotropin release and ovulation.[5] Furthermore, dydrogesterone does not affect the normal secretory transformation of endometrium, nor inhibit formation of progesterone in the placenta during early pregnancy.[6]

CHEMICAL PROPERTIES

- Dydrogesterone has a molecular formula of $C_{21}H_{28}O_2$ with molecular weight of 312.453 g/mol[4]
- Structural formula of dydrogesterone is closely related to progesterone and is demonstrated in Figure 1[1]
- Dydrogesterone is available as Duphaston film-coated tablets, each containing 10 mg of the drug and other pharmaceutical excipients like lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate and Opadry Y-1-7000 white [hypromellose, macrogol 400, titanium dioxide (E171)].[7]

Table 1: Types of progestins

Class	Preparation
Progesterone	Progesterone (micronized)
Retroprogesterone	**Dydrogesterone**
Progesterone derivative	Medrogestone
17α-hydroxyprogesterone derivatives (pregnanes)	Medroxyprogesterone acetate (MPA), megestrol acetate, chlormadinone acetate cyproterone acetate
19-norprogesterone derivatives (norpregnanes)	Demegestone, promegestone, trimegestone
17α-hydroxynorprogesterone derivatives (norpregnanes)	Nomegestrol acetate
19-nortestosterone derivatives (estranes)	Norethisterone = norethindrone, norethisterone acetate, lynestrenol
19-nortestosterone derivatives (gonanes)	Norgestrel, levonorgestrel, norgestimate

Based on information from: Campagnoli C, Clavel-Chapelon F, Kaaks R, *et al.* Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *J Steroid Biochem Mol Biol.* 2005;96(2):95–108..

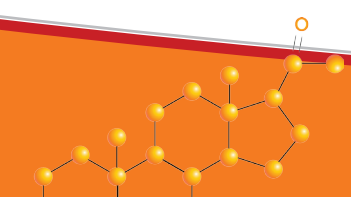
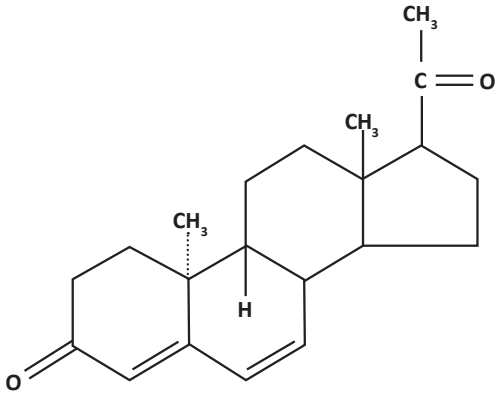


Figure 1: Molecular structure of dydrogesterone



Based on information from: Coelingh Bennink HJ, Boerrigter PJ. Use of dydrogesterone as a progestogen for oral contraception. *Steroids.* 2003;68(10-13):927-929.

INDICATIONS

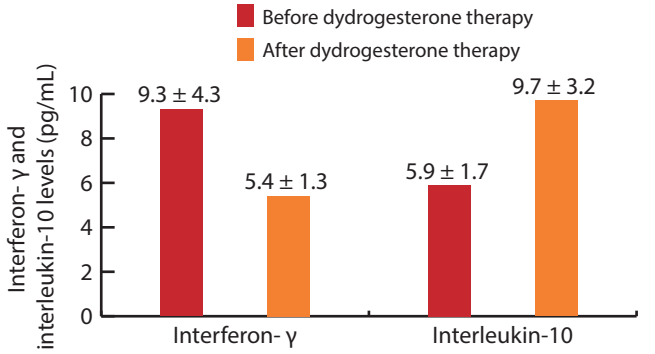
- Dydrogesterone is used in the treatment of infertility due to luteal phase insufficiency, dysmenorrhea, secondary amenorrhea, irregular menstrual cycles, premenstrual syndrome, threatened or recurrent miscarriage, abnormal uterine bleeding, pain in endometriosis and luteal phase support.[7,8]

PHARMACOLOGICAL EFFECTS

Effects on immunomodulation

- Immune-related cytokines are considered to play key roles in pregnancy. The two subsets of T helper (Th) cells i.e. Th1 and Th2 are associated with different patterns of cytokine production. Th1 cells are responsible for the production of interferon (IFN)-γ, tumor necrosis factor (TNF)- α and interleukin (IL)-2 while Th2 cells secrete the cytokines IL-4, IL-5, IL-6, IL-10, and IL-13[9]
- Evidence suggests that Th2-type maternal immunity results in successful pregnancy whereas Th1-type immunity can be harmful for fetal development and may even lead to pregnancy failure. A switch from Th1 to Th2 cytokine profile is considered to be beneficial.[9,10]
- Raghupathy *et al*[11] showed that dydrogesterone is able to induce such a maternal cytokine shift from Th1 to Th2 in women undergoing unexplained recurrent spontaneous miscarriage by inhibiting production of IFN-γ and TNF-α and up-regulating the synthesis of IL-4 and IL-6
- Similar results were obtained in another study[12] wherein dydrogesterone supplementation in women with threatened preterm delivery resulted in significant reduction in IFN-γ and marked increase in IL-10 levels (Figure 2)

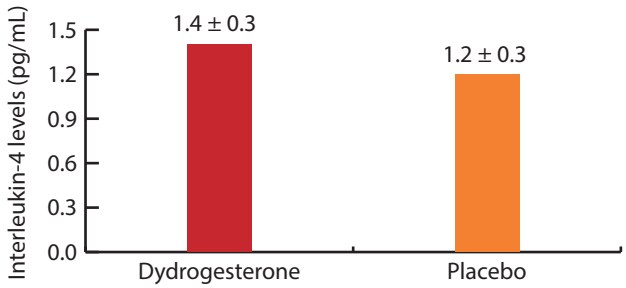
Figure 2: Effects of dydrogesterone supplementation on interferon-γ and interleukin-10 levels in women with threatened preterm delivery



Based on information from: Hudić I, Szekeres-Bartho J, Fatušić Z, *et al.* Dydrogesterone supplementation in women with threatened preterm delivery--the impact on cytokine profile, hormone profile, and progesterone-induced blocking factor. *J Reprod Immunol.* 2011;92(1-2):103-7.

- Findings of another double-blind, placebo controlled study[13] conducted in pregnant females with a history of recurrent miscarriages showed that use of dydrogesterone resulted in significantly higher levels of IL-4 in women who continued their pregnancy beyond 20 weeks of gestation (Figure 3).Therefore, dydrogesterone can improve pregnancy outcomes due to its favorable immunomodulatory effects.

Figure 3: Mean interleukin-4 levels in pregnant women (>20 weeks of gestation) with history of recurrent miscarriages following administration of dydrogesterone or placebo

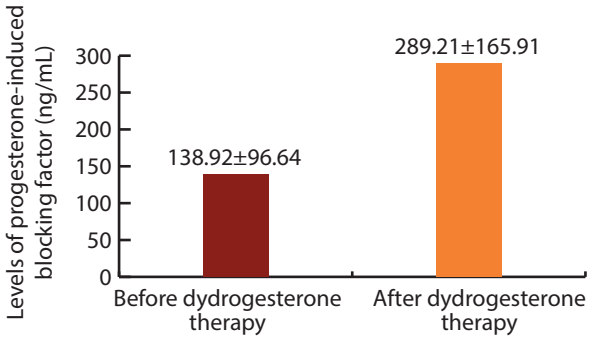


Based on information from: Kumar A, Begum N, Prasad S, *et al.* Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial. *Fertil Steril.* 2014;102(5):1357-1363.e3.

Progesterone-induced blocking factor formation

- Progesterone-induced blocking factor (PIBF) is considered to inhibit the inflammatory and thrombotic effects on the fetus by mediating the biological actions of progesterone and facilitating the maternal Th1 to Th2 cytokine shift[13]
- This agent also favours the production of asymmetric, pregnancy-protecting antibodies and inhibits the activity of natural killer cells. Low PIBF levels have been observed in pregnancies that end in miscarriages[13]
- It has been shown that dydrogesterone therapy is associated with significant increase in PIBF levels in pregnant women with risk of preterm delivery (Figure 4).[12] This in turn may suggest the positive role of dydrogesterone in improving pregnancy success rates.

Figure 4: Increase in levels of progesterone-induced blocking factor in pregnant women with risk of preterm delivery following dydrogesterone administration

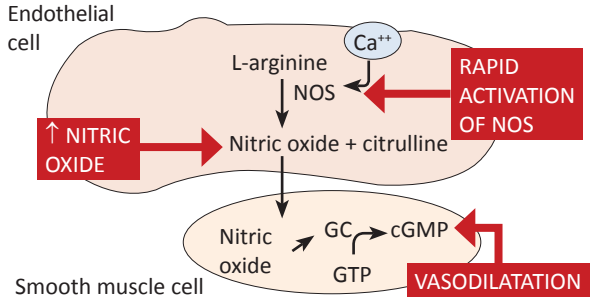


Based on information from: Hudić I, Szekeres-Bartho J, Fatušić Z, *et al.* Dydrogesterone supplementation in women with threatened preterm delivery the impact on cytokine profile, hormone profile, and progesterone-induced blocking factor. *J Reprod Immunol.* 2011;92(1-2):103-7.

Nitric oxide production

- Nitric oxide plays an important role in many biological systems including the uterus. It promotes vasodilatation, decidua formation and endometrial remodeling during trophoblast invasion along with regulation of endometrial functions like receptivity, implantation and menstruation[14]
- During pregnancy, progesterone-induced nitric oxide synthesis results in improved vascularity by decreasing uteroplacental vascular resistance[14]
- Dydrogesterone is considered to upregulate endothelial nitric oxide synthase expression through myometrial quiescence and immunomodulatory effects[14]
- The mechanism of action of nitric oxide and effects of dydrogesterone on its production is shown in Figure 5.[14,15]

Figure 5: Effects of dydrogesterone on nitric oxide production



Abbreviations: : NOS- nitric oxide synthase, GC- guanylate cyclase, GTP- guanosine triphosphate, cGMP- cyclic guanosine monophosphate

Based on information from: 1. Ghosh S, Chattopadhyay R, Goswami S, *et al.* Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: a pilot study. *J Obstet Gynaecol Res.* 2014;40(7):1871-6, **2.** Galley HF, Webster NR. Physiology of the endothelium. *BJA.* 2004;93(1):105-113.

Androgenic and anti-androgenic effects

- It has been shown that the anti-androgenic potential of dydrogesterone and its main metabolite 20-α-dihydrodydrogesterone is less prominent in comparison to progesterone.[16]

Effects on lipid profile

- Evidence suggests that continuous combined hormone replacement therapy (HRT) comprising of estrogen and progestogen improves the lipid profile in postmenopausal women. However, addition of some progestogens has been shown to nullify the beneficial effects of estrogens in improving the lipid profile. No such negative effects are seen when dydrogesterone is used in a combined HRT regimen
- A 6-month study showed that oral 17β-estradiol combined with dydrogesterone has beneficial effects on the lipid and lipoprotein profile in postmenopausal women.[17]

PHARMACOKINETIC PROFILE

- Dydrogesterone is highly active after oral administration
- It is very rapidly absorbed and then metabolized, chiefly to 20-α-dihydrodydrogesterone which achieves the highest concentration after 0.5-2.5 hours[7]
- Dydrogesterone has a bioavailability of 28% which is greater than that of progesterone[18]

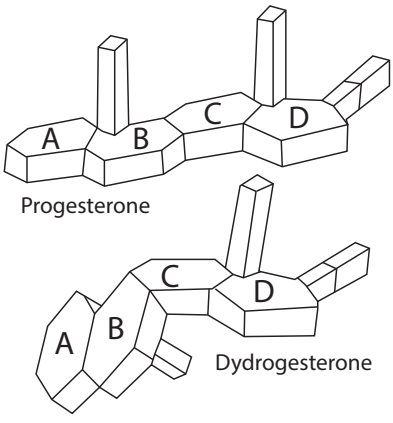
- The mean half-life of dydrogesterone is 5-7 hours, and DHD is 14-17 hours
- About 80% of the drug is excreted in urine after 24 hours of administration and it is completely excreted within 72 hours.[5,7]

DYDROGESTERONE- THE UNIQUE PROGESTIN

Uniqueness in structure

- The structural formula of dydrogesterone is closely related to progesterone
- The difference in structure is provided by an additional double bond between C6 and C7 (4,6-dien-3-one configuration)
- Dydrogesterone has a methyl group at carbon 10 but is not acetylated
- A 9β, 10α retro structure exists which means that the methyl group at carbon 10 in dydrogesterone is located in α position instead of β position in progesterone. This retro structure prevents the enzymatic reduction of the double bonds
- Compared to progesterone which has an almost flat molecular structure, the reversed configuration in dydrogesterone results in a bent spatial geometry in which the plane of rings A and B are orientated at an angle of 60° angle with the rings C and D (Figure 6)
- The C6–C7 double bond constricts dydrogesterone into a rigid conformation and makes it suitable for binding with the PR.[5,7,18]

Figure 6: Schematic representation of the chemical structures of progesterone and dydrogesterone showing the retrosteroid spatial configuration of dydrogesterone



Based on information from: Kuhl H. Pharmacology of Progestogens. *J Reproduktionsmed Endokrinol.* 2011;8 (Special Issue 1):157–76.

Receptor selectivity and binding affinity

- Dydrogesterone has been shown to bind exclusively to the PRs with a relative binding affinity of 15.9% (relative to progesterone)[19]
- Dydrogesterone does not bind to the estrogen, androgen or glucocorticoid receptors and hence it has no estrogenic, androgenic and glucocorticoid activities[19]
- Although it has similar agonistic activity to progesterone for PR type B, the agonistic activity for PR type A is found to be relatively weaker. This selectivity for PR type B

Table 3: Differences between dydrogesterone and progesterone

Parameter	Dydrogesterone	Progesterone
Class[A]	Retroprogesterone	Progestin
Structure » Methyl group at carbon 10[B] » Bond between carbon 6 and 7[B] » Molecular structure[C]	 » α position » Double bond » Bent	 » β position » Single bond » Flat
Selectivity for progesterone B type receptor[D]	Greater	Less
Doses (mg)[B]	10	100, 200, 300
Bioavailability (%)[B]	28	<5
Effects on ovulation[C]	Absent	Present
Antigonadotropic effects[C]	Absent	Present
Antiandrogenic effects[C]	Absent	Present
Glucocorticoid effects[C]	Absent	Present
Excretion in urine as pregnanediol[E]	Absent	Present
Thermogenic effect[C]	Absent	Present during ovulation

Based on information from: A) Campagnoli C, Clavel-Chapelon F, Kaaks R, *et al.* Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *J Steroid Biochem Mol Biol.* 2005;96(2):95–108. **B)** Stanczyk FZ, Hapgood JP, Winer S, Mishell DR. Progestogens Used in Postmenopausal Hormone Therapy: Differences in Their Pharmacological Properties, Intracellular Actions, and Clinical Effects. *Endocr Rev.* 2013;34(2):171–208. **C)** Kuhl H. Pharmacology of Progestogens. *J Reproduktionsmed Endokrinol.* 2011;8 (Special Issue 1):157–76. **D)** Cabeza M, Heuze Y, Sánchez A, *et al.* Recent advances in structure of progestins and their binding to progesterone receptors. *J Enzyme Inhib Med Chem.* 2015;30(1):152-9. **E)** Duphaston prescribing information.

confer therapeutic advantages in the form of enhanced progestogenic effects[19]

- Dydrogesterone acts as an inhibitor of 5α-reductase type 2 (5α-R2) enzyme along with 17-β-hydroxysteroid dehydrogenase (17-β-HSD) types 3 and 5, hence inhibiting androgenic activity[19]
- Dydrogesterone's structural alterations and receptor selectivity results in improved biological effects.[19]

Stability and bioavailability

- Enhanced configuration of dydrogesterone results in its increased stability and hence higher bioavailability with less collateral effects[20]
- Dydrogesterone exhibits quick onset of action reaching peak absorption levels within 30 minutes and demonstrates progestational activity with relatively lower doses.[20]

Differences from progesterone

- Compared with progesterone, dydrogesterone has a greater affinity for the PRs and can be used at lower oral doses to promote endometrial proliferation owing to its better bioavailability and to the progestogenic activity of its metabolites.[18] Unlike progesterone, it has no anti-androgenic or glucocorticoid effects[5]
- Dydrogesterone has no inhibitory effects on ovulation when administered throughout the menstrual cycle and does not have its thermogenic effect[18]
- In contrast to progesterone, dydrogesterone is not excreted in urine as pregnanediol therefore making evaluation of endogenous progesterone production based on pregnanediol excretion possible[7]
- The differences between dydrogesterone and progesterone are demonstrated in Table 3.

CLINICAL EXPERIENCE

Recurrent miscarriages

Spontaneous pregnancy loss is a common occurrence affecting about 15% of the total clinically recognized pregnancies. Recurrent pregnancy loss (RPL) also referred to as recurrent miscarriage or habitual abortion can be defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period; affecting about 1-2% of women.[21]

RANDOMIZED CONTROLLED TRIAL

STUDY 1

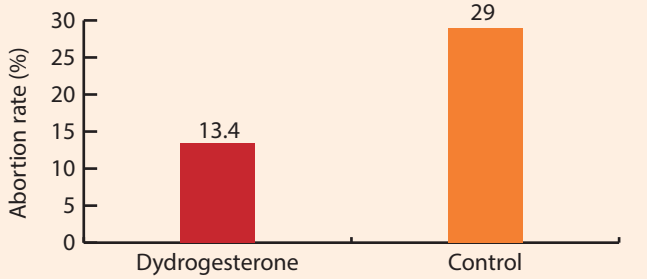
Aim

To evaluate the role of dydrogesterone in reducing recurrent spontaneous abortion.

Method

Study enrolled 180 women with history of recurrent, unexplained spontaneous abortion and were randomized to receive oral dydrogesterone (10 mg b.i.d.), intramuscular human chorionic gonadotrophin (hCG; 5000 IU every 4 days) or no additional treatment (controls), and treatment was continued until the 12th gestational week.

Figure 7: Dydrogesterone reduces recurrent spontaneous abortion



Based on information from: El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. *J Steroid Biochem Mol Biol.* 2005;97(5):431-4.

Results

Abortions were significantly less common in the dydrogesterone group (13.4%) than in the control group (29%) (Figure 7). No significant diffrence between hCG and control groups.

Conclusion

Hormonal support with dydrogesterone can increase the chances of a successful pregnancy in women with a history of recurrent spontaneous abortion.[22]

RANDOMIZED CONTROLLED TRIAL

STUDY 2

Aim

To evaluate the impact of administration of dydrogesterone in early pregnancy on pregnancy outcome.

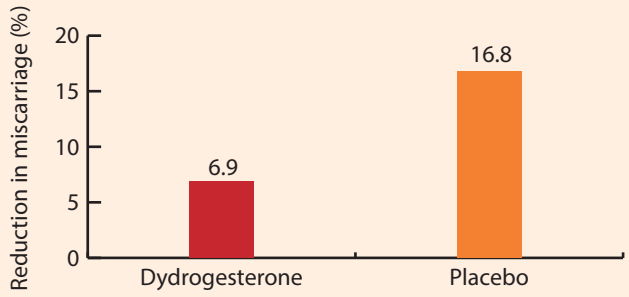
Method

Study enrolled women with either: [1] a history of idiopathic recurrent pregnancy loss (RPL), in either dydrogesterone (20 mg/day from confirmation of pregnancy to 20 weeks of gestation) or placebo, or [2] no history of miscarriage.

Result

Risk of occurrence of miscarriage after 3 abortions was 2.4 times higher in the placebo group vs. the treatment group (risk ratio=2.4, 95% CI=1.3-5.9). Additionally, statistically significant decrease in number of miscarriages was observed with dydrogesterone group when compared with placebo group (6.9% vs. 16.8%) (Figure 8).

Figure 8: Dydrogesterone significantly reduces rate of miscarriage



Based on information from: Kumar A, Begum N, Prasad S, *et al.* Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial. Fertil Steril. 2014;102(5):1357-1363.e3.

Conclusion

The study supported dydrogesterone use in women with recurrent abortions to improve pregnancy outcome. Moreover, dydrogesterone administration showed a trend reducing the number of preterm deliveries, cesarean delivery , low-birth weight babies and small-for-date babies.[13]

PILOT STUDY

STUDY 3

Aim

To assess differences in uteroplacental blood flow and pregnancy outcome in women with idiopathic recurrent spontaneous miscarriage (ISRM).

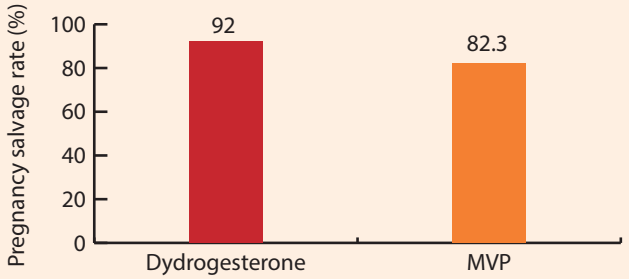
Method

Study randomized 133 women (aged 23–40 years) with history of early miscarriages and spontaneous conception into oral dydrogesterone (group A, n = 51) and micronized vaginal progesterone (group B, n = 50). Outcome measures consist parameter of endometrial blood flow by ongoing pregnancy rate and doppler indices.

Result

After progesterone supplementation, groups A and B showed highly significant reduction in resistivity index, pulsatility index and an increase in end diastolic velocity. An increase in Peak systolic velocity value recorded in group A than group B. Systolic/diastolic ratio showed remarkable difference between both groups. Pregnancy salvage rates were higher in groups A (92.0%) than group B (82.3%) (Figure 9).

Figure 9: Higher pregnancy salvage rate with dydrogesterone therapy as compared to micronized vaginal progesterone



Based on information from: Ghosh S, Chattopadhyay R, Goswami S, *et al.* Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: A pilot study. *J Obstet Gynaecol Res.* 2014;40(7):1871–1876.

Conclusion

Oral dydrogesterone appears to be non inferior to progesterone in improving endometrial blood flow. In addition, progesterone supplementation appears to lower vascular resistance in women with IRSM.[14]

SYSTEMATIC REVIEW

STUDY 4

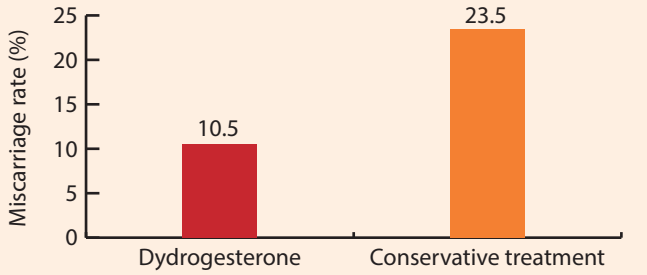
Aim

To evaluate the efficacy of the orally acting progestagen, dydrogesterone in lowering the incidence of subsequent miscarriage in women with recurrent miscarriage.

Method

Eligible candidates for the study included 509 pregnant women who were randomized into dydrogesterone (10 mg b.i.d)and standard bed rest or placebo intervention, respectively. Dydrogesterone was administered at a dose of 20 mg/day for 20 weeks in 175 patients and for 8 weeks in 82 patients.

Figure 10: Lower abortion rate with dydrogesterone therapy as compared to conservative therapy



Based on information from: Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage. *Gynecol Endocrinol.* 2015;31(6):422-30.

Result

The miscarriage rate after dydrogesterone administration (10.5%) was considerably lower than women treated with conservative treatment (23.5%) (13% absolute reduction in the miscarriage rate) (Figure 10).

Conclusion

Authors thus concluded that dydrogesterone administration yields significant reduction of 29% in the odds for miscarriage compared to standard care indicating a real treatment effect.[23]

Threatened miscarriages

The World Health Organization (WHO) defines threatened miscarriages as pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy without cervical dilatation.[24] For treating threatened miscarriages; dydrogesterone, when administered orally, has been found to be efficacious because it enhances implantation, prevents myometrial contractility and prevents cervical dilatation. Activation of progesterone receptors on lymphocytes results in the synthesis of a protein known as PIBF, which favors production of asymmetric, pregnancy-protecting antibodies.[25]

RANDOMIZED CONTROLLED TRIAL

STUDY 1

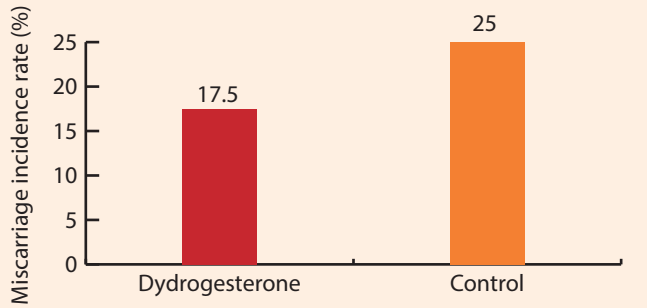
Aim

To determine role of dydrogesterone in preserving pregnancy in women with threatened miscarriage.

Method

Eligible candidates (n=146) with history of mild or moderate vaginal bleeding during the first trimester of pregnancy were randomized to receive oral dydrogesterone (10 mg b.i.d.) (n=86) or no treatment (n=60). Dydrogesterone was continued until one week after the bleeding stopped.

Figure 11: Dydrogesterone administration showed marked reduction in incidence of miscarriage



Based on information from: El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. *Maturitas.* 2009;65 Suppl 1:S43-6.

Result

Dydrogesterone group recorded marked reduction in incidence of miscarriage than in the untreated group (17.5% vs. 25%) (Figure 11).

Conclusion

Dydrogesterone appears to have beneficial effects in women with threatened miscarriage.[26]

RANDOMIZED CONTROLLED TRIAL

STUDY 2

Aim

To determine whether dydrogesterone therapy in threatened abortion during the first trimester of pregnancy can improve pregnancy outcome.

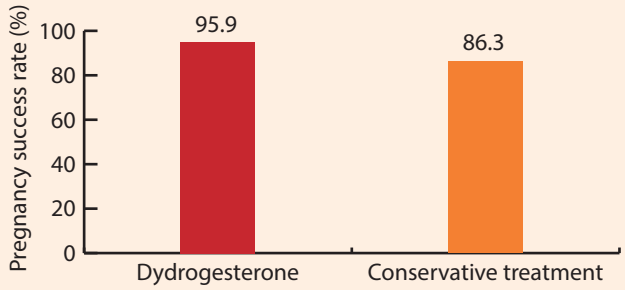
Methods

Women (n=154) with vaginal bleeding before 13 weeks gestation were randomized to receive either dydrogesterone 40 mg stat dose followed by 10 mg twice a day for one week or conservative therapy.

Results

Dydrogesterone group recorded higher pregnancy success rate (95.9%) compared with women who received conservative treatment (86.3%) (Figure 12).

Figure 12: Higher pregnancy success rate with dydrogesterone than conservative treatment



Based on information from: Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. *J Steroid Biochem Mol Biol.* 2005;97(5):421-5.

Conclusion

Thus, dydrogesterone can reduce the incidence of pregnancy loss in threatened abortion during the first trimester in women without a history of recurrent abortion.[27]

SYSTEMATIC REVIEW

STUDY 3

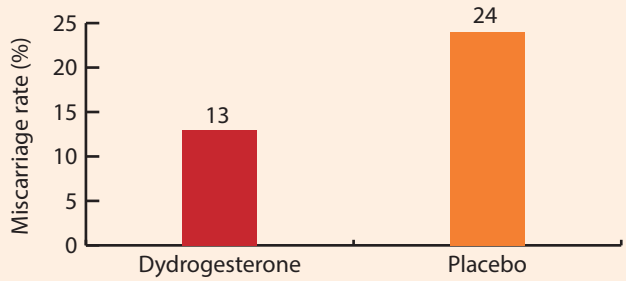
Aim

To assess whether the orally acting progesterone, dydrogesterone lowers the incidence of miscarriage in women with threatened miscarriage.

Method

A total of 21 reports involving 1380 patients who were on dydrogesterone treatment were identified. Among them, only 5 randomized trials including 660 women met the criteria and number of subsequent miscarriages or continuing pregnancies per randomized woman was compared in women receiving dydrogesterone (n=335) compared to standard bed rest or placebo intervention (n=325).

Figure 13: Lower miscarriage rate with dydrogesterone as compared to placebo



Based on information from: Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage. *Gynecol Endocrinol.* 2012;28(12):983-990.

Results

Miscarriage rate recorded after dydrogesterone administration and control group were 13% and 24% (Figure 13).

Conclusion

A significant reduction of 47% in the odds for miscarriage after dydrogesterone compared to standard care was observed; indicating a real treatment effect.[25]

META-ANALYSIS

STUDY 4

Aim

To evaluate the influence of oral dydrogesterone and vaginal progesterone on threatened abortion.

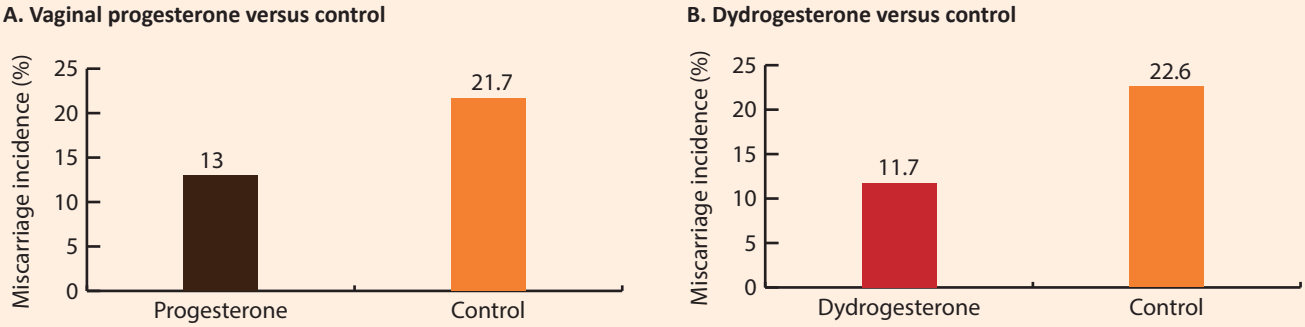
Method

Study recruited 913 pregnant women (including 322 treated with oral dydrogesterone, 213 treated with vaginal progesterone, and 378 control subjects).

Results

Incidence of miscarriage was significantly lower in the vaginal progesterone and oral dydrogesterone groups than in the control group (13.0% versus 21.7%, p=0.001) and (11.7% versus 22.6%, p=0.001) (Figure 14), respectively.

Figure 14: Lower miscarriage incidence with dydrogesterone and progesterone as compared to control group



Based on information from: Lee HJ, Park TC, Kim JH, Norwitz E, Lee B. The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2017;2017:3616875.

Conclusion

Thus, study posited that progesterone therapy; particularly, oral dydrogesterone can be effective to prevent miscarriage in pregnant women experiencing threatened abortion.[28]

Luteal phase support

Luteal phase defect is an iatrogenic phenomenon of controlled ovarian stimulation (COS) with multifollicular development and oocyte retrieval for *in vitro* fertilization (IVF). Herein, from decades dydrogesterone has been in use for exogenous support of endogenous progesterone production by the corpus luteum and placenta, thus providing luteal phase support (LPS).[29,30]

RANDOMIZED CONTROLLED TRIAL

STUDY 1

Aim

To compare oral dydrogesterone 30 mg daily (10 mg three times daily [TID]) to micronized vaginal progesterone (MVP) 600 mg daily (200 mg TID) for LPS in IVF.

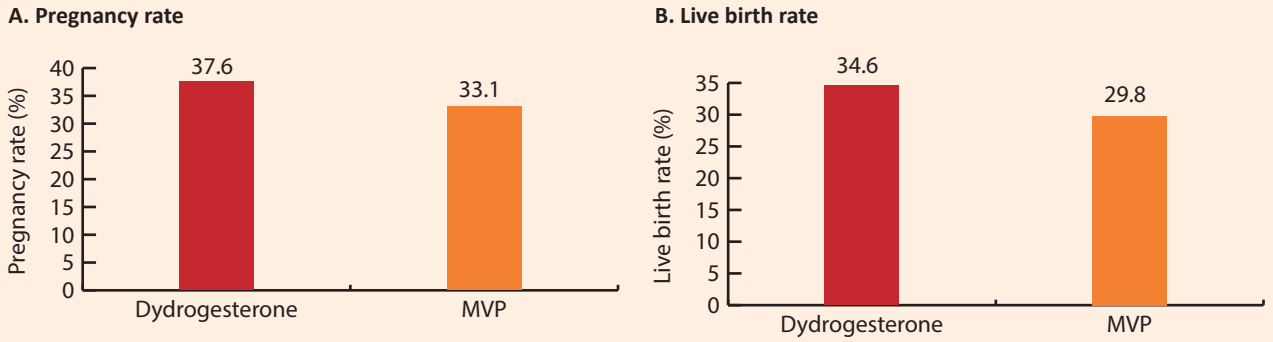
Method

Study enrolled 1031 premenopausal women with history of infertility who were planning to undergo IVF and randomized into either oral dydrogesterone (n = 520) or MVP (n = 511).

Results

Oral dydrogesterone showed similar efficacy as MVP. The pregnancy rate with oral dydrogesterone and MVP treatment groups at 12 weeks of gestation was recorded 37.6% and 33.1%, respectively. Similarly, live birth rate with oral dydrogesterone and MVP treatment groups was 34.6% and 29.8%, respectively (Figure 15).

Figure 15: Oral dydrogesterone is non-inferior to micronized vaginal progesterone (MVP)



Based on information from: Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization. *Hum Reprod.*2017;32(5):1019–1027.

Conclusion

Oral dydrogesterone may replace MVP for luteal phase support in IVF, attributing to the oral route being more patient-friendly than intravaginal administration, as well as it being a well tolerated and efficacious treatment.[31]

STUDY 2

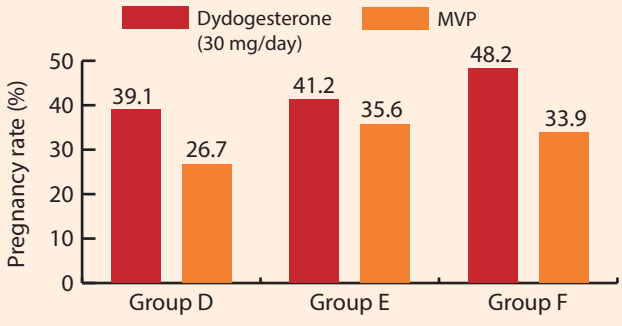
Aim

To evaluate dydrogesterone for LPS in assisted reproductive technologies (ART) (Phase I) and to compare it with MVP (Phase II).

Method

In phase I, study divided 498 patients into long protocol and not at risk of ovarian hyperstimulation syndrome (OHSS) (group A); long protocol and at risk of OHSS (group B); and those in a donor oocyte program (group C) and randomized them into dydrogesterone 20 mg/day (n = 218) or placebo (n = 280). In phase II, the same three groups (n = 675; groups D, E and F) were randomized to dydrogesterone 30 mg/day (n = 366) or micronized progesterone (MVP) 600 mg/day (n = 309).

Figure 16: Dydrogesterone showed higher pregnancy rate when compared with micronized progesterone (MVP)



Based on information from: Patki A, Pawar VC. Modulating fertility outcome in assisted reproductive technologies by the use of dydrogesterone. *Gynecol Endocrinol.* 2007;23 Suppl 1:68-72.

Result

In phase II, dydrogesterone showed higher rates of pregnancy when compared with MVP: group D: 39.1% vs. 26.7% , group E: 41.2% vs. 35.6% and group F: 48.2% vs. 33.9% (Figure 16).

Conclusion

Thus, study concluded that dydrogesterone is an effective drug in LPS in ART.[32]

Endometriosis

Ample studies substantiate that GnRH agonist therapy used in post-operative treatment of endometriosis can improve disease-related symptoms and inhibit relapse. In addition, to reduce or prevent hypoestrogenic state caused by long-term use of GnRHa; low doses of estrogen and progestogen can be combined in the treatment in a process called "add-back therapy". [33]

RANDOMIZED CONTROLLED TRIAL

STUDY 1

Aim

To assess the efficacy and safety of dydrogesterone in the post-laparoscopic treatment of endometriosis in Indian patients.

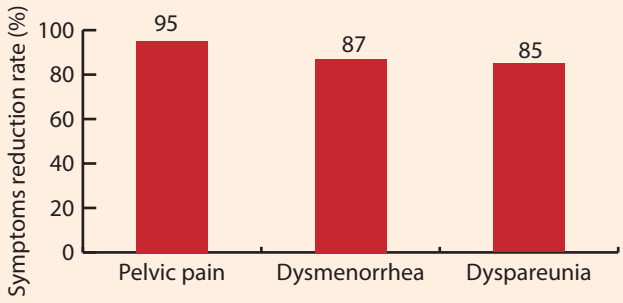
Method

Study included 98 endometriosis patients who had undergone laparoscopy and were treated with dydrogesterone 10 mg/day (or 20 mg/day in severe cases) orally from day 5 to day 25 of each cycle for 3–6 months.

Result

Findings presented significant reduction in pelvic pain (95%), dysmenorrhea (87%) and dyspareunia (85%), respectively by the end of the 6th cycle (Figure 17). A total of 21.1% of the patients were considered cured and 66.7% showed improvement. Overall, dydrogesterone therapy was rated as excellent to good by 74% of patients and 70% of physicians.

Figure 17: Dydrogesterone significantly reduces rate of symptoms in endometriosis patients by the end of 6th cycle



Based on information from: Trivedi, Selvaraj P, Kamala. *et al*. Effective post-laparoscopic treatment of endometriosis with dydrogesterone. *Gynecol Endocrinol*.2007;23:sup1, 73-76.

Conclusion

The investigators concluded that dydrogesterone is an effective and safe post-laparoscopic treatment for endometriosis.[34]

Safety and tolerability

- **Oral dydrogesterone is considered to be equally efficacious and safe as micronized vaginal progesterone (MVP) for luteal phase support during *in vitro* fertilization (IVF) procedures**
- Results of the **Lotus Study I** showed oral dydrogesterone to be non-inferior to MVP as pregnancy rate and live birth rates in both groups were comparable. Also, oral dydrogesterone was well-tolerated and had a safety profile that was similar to that of MVP. Rate of maternal adverse events in the dydrogesterone and MVP groups were 10.8% and 13.3%, respectively (Table 4)
- **Therefore, oral dydrogesterone appears to be an effective and well-tolerated treatment option for luteal phase support during IVF and it may replace MVP as the standard of care as it has the additional advantage of being more patient-friendly due to the oral route of administration.**[31]

Table 4: Findings of Lotus study

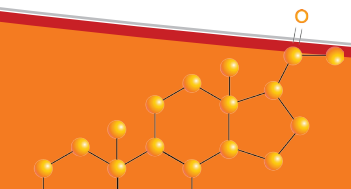
Parameters	Dydrogesterone	Micronized vaginal progesterone
Pregnancy rate (%)	37.6	33.1
Live birth rate (%)	34.6	21.9
Neonates with no abnormality (%)	93.4	92.4

Based on information from: Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization. *Human Reprod*.2017;32(5):1019–1027.

SCIENTIFIC EVIDENCES TO REINFORCE DYDROGESTERONE SUPERIORITY ACROSS CORE INDICATIONS

Study	Design	Treatment arms	Outcome measures/ study endpoints
RECURRENT MISCARRIAGES			
A systematic review of dydrogesterone for the treatment of recurrent miscarriage[22] *Gynecol Endocrinol. 2015;31(6):422-30*	Systematic review (Total number of patients (N)=509)	Dydrogesterone compared to standard bed rest or placebo intervention	Significant reduction of 29% in the odds for miscarriage when dydrogesterone is compared to standard care indicating a real treatment effect
Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production[13] *Fertil Steril. 2014;102(5):1357-1363*	Double-blind, randomized, parallel, placebo-controlled trial (N=347)	Women with either: [1] a history of idiopathic recurrent pregnancy loss (RPL)(N=173), in either a dydrogesterone group (20 mg/day) or a placebo group, or [2] no history of miscarriage (control, N=174)	Risk of occurrence of miscarriage after 3 abortions was 2.4 times higher in the placebo group vs. the treatment group
Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage[14] *J Obstet Gynaecol Res. 2014;40(7):1871–1876*	Pilot study (N=133)	Oral dydrogesterone (group A, N = 51) compared to micronized vaginal progesterone (group B, N = 50) for luteal support Pregnant women without history of recurrent miscarriage served as controls (group C, N= 32)	Oral dydrogesterone appears to be equally effective in improving endometrial blood flow as compared with micronized progesterone
Dydrogesterone in the reduction of recurrent spontaneous abortion[23] *J Steroid Biochem Mol Biol. 2005;97(5):431-4*	Randomized controlled trial (N= 180)	Oral dydrogesterone (10 mg b.i.d.), intramuscular human chorionic gonadotrophin (hCG; 5000 IU every 4 days) or no additional treatment (controls)	Hormonal support with dydrogesterone can increase the chances of a successful pregnancy in women with a history of recurrent spontaneous abortion
THREATENED MISCARRIAGES			
A systematic review of dydrogesterone for the treatment of threatened miscarriage[25] *Gynecol Endocrinol, 2012; 28(12): 983–990*	Systematic review (N=660)	Dydrogesterone compared to standard bed rest or placebo intervention	Significant reduction of 47% in the odds for miscarriage when dydrogesterone is compared to standard care indicating a real treatment effect
Dydrogesterone support in threatened miscarriage[26] *Maturitas. 2009;65 Suppl 1:S43-6*	Systematic review (N=146)	Oral dydrogesterone (10 mg b.i.d.) (N=86) or no treatment (N=60)	Dydrogesterone appears to have beneficial effects in women with threatened miscarriage
Dydrogesterone in threatened abortion: pregnancy outcome[27] *J Steroid Biochem Mol Biol. 2005;97(5):421-5*	Systematic review (N=154)	Dydrogesterone 40 mg stat dose followed by 10 mg twice a day for one week or conservative therapy	Corpus luteal support with dydrogesterone has been shown to reduce the incidence of pregnancy loss in threatened abortion

The influence of oral dydrogesterone and vaginal progesterone on threatened abortion[28] *Biomed Res Int 2017;3616875:1-10*	Systematic Review and Meta-Analysis (N=913)	Oral dydrogesterone (N=322) and vaginal progesterone (N=213), versus control subjects (N=378)	Progesterone therapy, especially oral dydrogesterone, can effectively prevent miscarriage in pregnant women experiencing threatened abortion
LUTEAL PHASE SUPPORT			
A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization[31] *Human Reprod. 2017;32(5):1019–1027*	Randomized controlled trial (N=1031)	Oral dydrogesterone (N= 520) or micronized vaginal progesterone (MVP) (N=511)	Oral dydrogesterone may replace MVP as the standard of care for luteal phase support in IVF, owing to the oral route being more patient-friendly than intravaginal administration
Oral dydrogesterone vs. vaginal progesterone capsules for luteal phase support in women undergoing embryo transfer[35] *JBRA Assist Reprod. 2018;22(2):148-156*	Systematic review and meta-analysis	Dydrogesterone and progesterone were compared	Oral dydrogesterone provides at least similar reproductive outcomes than vaginal progesterone capsules when used for LPS in women undergoing embryo transfers
Comparison of oral dydrogesterone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing *in vitro* fertilization[36] *Fertil Steril. 2011 ;95(6):1961-5*	Randomized clinical study (N=1,373)	Micronized P gel, P capsule, and oral dydrogesterone were administered for luteal support and compared	Oral dydrogesterone seems to be a promising drug for luteal support in woman undergoing IVF
Modulating fertility outcome in assisted reproductive technologies by the use of dydrogesterone[32] *Gynecol Endocrinol. 2007;23 Suppl 1:68-72*	Randomized controlled trials Phase I: N=498 Phase II: N=675	Phase I: All patients received micronized progesterone 600 mg/day, vaginally Dydrogesterone 20 mg/day (N=218) or placebo (N=280) Phase II: Dydrogesterone 30 mg/day (n = 366) or micronized progesterone 600 mg/day (n = 309)	Dydrogesterone is effective in luteal-phase support in assisted reproductive technologies
Oral dydrogesterone versus intravaginal micronized progesterone as luteal phase support in assisted reproductive technology (ART) cycles[28] *J Steroid Biochem Mol Biol. 2005;97(5):416-20*	Randomized study (N=430)	Luteal supplementation with either intravaginal micronized progesterone 200 mg three times daily (N=351) or oral dydrogesterone 10 mg twice daily (N=79)	Significantly, more patients given dydrogesterone than micronized progesterone were satisfied with the tolerability of their treatment
ENDOMETRIOSIS			
Effective post-laparoscopic treatment of endometriosis with dydrogesterone[34] *Gynecol Endocrinol. 2007;23 Suppl 1:73-6.*	Open, multicenter study (N=98)	Dydrogesterone 10 mg/day (or 20 mg/day in severe cases) orally from day 5 to day 25 of each cycle for 3–6 months	Dydrogesterone is an effective and safe post-laparoscopic treatment for endometriosis



I. CARE AND TREATMENT OF COUPLES WITH RECURRENT PREGNANCY LOSS-EUROPEAN SOCIETY OF HUMAN REPRODUCTION AND EMBRYOLOGY (ESHRE) GUIDELINES, 2017

Miscarriage or pregnancy loss may be defined as the spontaneous termination of a pregnancy before the fetus attains viability. The loss of two or more pregnancies is termed as recurrent pregnancy loss (RPL) and it has a considerable emotional impact on women and their partners. Repetitive nature of RPL may intensify the feelings of loss and grief and the sense of personal failure. Guideline of the European Society of Human Reproduction and Embryology (ESHRE) offers advice on the care of couples coping with RPL and treatment recommendations for RPL.

Recommendation 1: Couples with RPL should be informed about the detrimental effect of smoking, alcohol consumption, obesity and excessive exercise on their chances of a live birth; therefore, smoking cessation, striving for a normal body weight, limited consumption of alcohol and a normal exercise pattern is recommended in couples with RPL.

Recommendation 2: All couples with results of an abnormal fetal or parental karyotype should be offered genetic counseling.

Recommendation 3: During preconception counseling, women with RPL could be advised to consider prophylactic vitamin D supplementation.

Recommendation 4: During early stages of pregnancy, vaginal progesterone has no beneficial effect in women with unexplained RPL. However, some evidence suggests the efficacy of oral dydrogesterone initiated during early stages when fetal heart action can be confirmed.

Source: Recurrent Pregnancy Loss: Guideline of the European Society of Human Reproduction and Embryology. Available at: https://www.eshre.eu/~/media/sitecore-files/Guidelines/Recurrent-pregnancy-loss/ESHRE-RPL-Guideline_28112017_FINAL.pdf. Accessed on 06/08/2018.

II. PREVENTION AND TREATMENT OF THREATENED OR RECURRENT MISCARRIAGE WITH PROGESTOGENS-EUROPEAN PROGESTIN CLUB GUIDELINES, 2015

Progesterone, the leading pregnancy hormone, is vital for conception and implantation. It is also important throughout pregnancy until term. The duration between 8th and 12th weeks of gestation is critical since this is the period wherein production and secretion of progesterone is taken over by the placenta from the corpus luteum. This period, also known as luteoplacental shift, may witness a plateau or a fall in circulating endogenous progesterone, which may clinically manifest with symptoms of threatened or recurrent (habitual) miscarriages. Moreover, certain cases of ovulation induction are associated with a rapid fall in progesterone level from an initial high level, which induces a progesterone withdrawal bleed and clinically manifests with signs of threatened miscarriage. In this context,

progestogen supplementation has emerged as an effective and reliable method for prevention and treatment of threatened or recurrent (habitual) miscarriage.

Treatment approach in women with threatened miscarriage

Accumulating evidence suggests that the use of progestogen, specifically dydrogesterone, in women clinically diagnosed with threatened miscarriage, is more effective in reducing the rate of spontaneous miscarriage than a placebo or no therapy. Moreover, it is also suggested to recompense for the critical luteoplacental progesterone shift. A systematic large meta-analysis on dydrogesterone comprising 660 participants demonstrated a statistically significant reduction with dydrogesterone in the odds ratio for miscarriage as compared to the standard care.

Recommendation 1: Dydrogesterone is associated with a reduction in the rate of spontaneous miscarriage in women clinically diagnosed with threatened miscarriage.

Treatment approach in women with a history of recurrent (habitual) miscarriage

There is a growing body of evidence that suggests that progestogen, specifically dydrogesterone, is more effective in reducing the rate of miscarriage in women presenting with a history of three or more recurrent miscarriages. A double-blind, randomized, parallel group, placebo-controlled study comprising 360 women with a history of three first-trimester pregnancy losses substantiated the same. Herein, a lower miscarriage rate was observed with dydrogesterone (6.9%) as compared to placebo (16.8%). Besides, dydrogesterone therapy was also associated with a higher mean gestational age at delivery.

Recommendation 2: Dydrogesterone reduces the rate of miscarriage in women presenting with a clinical diagnosis of ≥3 recurrent miscarriage.

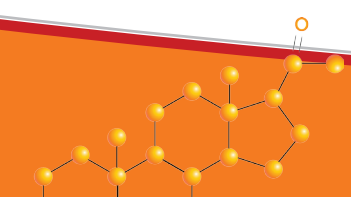
Source: Schindler AE, Carp H, Druckmann R, *et al.* European Progestin Club Guidelines for prevention and treatment of threatened or recurrent (habitual) miscarriage with progestogens. *Gynecol Endocrinol.* 2015;31(6):447-9.

III. USE OF PROGESTOGENS IN ASSISTED REPRODUCTIVE TECHNIQUES, RECURRENT PREGNANCY LOSS AND THREATENED MISCARRIAGE-FEDERATION OF OBSTETRIC & GYNECOLOGICAL SOCIETIES OF INDIA (FOGSI 2015)

Progesterone is an important hormone required to maintain pregnancy. Dydrogesterone (6-dehydro-retroprogesterone) is a progestogen, which exhibits high affinity, particularly for progesterone receptors; it has no affinity for androgen, mineralocorticoid, glucocorticoid, and estrogen receptors. Dydrogesterone shares close resemblance to the endogenous progesterone, both in its molecular structure as well as in pharmacological effects.

Role of dydrogesterone in luteal support in assisted reproductive techniques (ART)

- Adequate luteal support is needed during ART to enhance implantation and pregnancy rates, which can be accomplished by using progesterone
- Deficiency of endogenous progesterone is associated with implantation failure and early miscarriages
- It is recommended that progesterone supplementation be initiated just after oocyte retrieval/embryo transfer



- Based on available evidence on progesterone supplementation in ART cycles, dydrogesterone: 20-30 mg/day orally can be administered.

Role of dydrogesterone in recurrent pregnancy loss and threatened miscarriage

- Dydrogesterone is shown to exhibit immunomodulatory characteristics, such as decreasing pro-inflammatory and increasing anti-inflammatory cytokines in early pregnancy
- Available clinical data suggest that progesterone support, such as through dydrogesterone supplementation, is beneficial in women presenting with a clinical diagnosis of threatened miscarriage (Table 1).

Table 1: Dosage of dydrogesterone in different clinical indications

Indication	Drug	Dosage
Recurrent miscarriage	Oral dydrogesterone	10 mg twice daily till 20 weeks of pregnancy
Threatened miscarriage	Oral dydrogesterone	40 mg loading dose followed by 20-30 mg/day till 7 days after bleeding stops

Source: FOGSI Position Statement on the Use of Progestogens. Available at: http://www.fogsi.org/wp-content/uploads/2017/07/Progesterone-position-paper-Oct-2015.pdf. Accessed on 04/08/2018.

SUMMARY

- Dydrogesterone is a potent retroprogesterone that has been utilized in about 94 million patients and 20 million pregnancies in more than 100 countries for over 55 years[37]
- Dydrogesterone is considered to act on progesterone receptors in the uterus and promote healthy growth and normal shedding of the endometrial lining[4]
- The agent does not exhibit any estrogenic, androgenic or anti-androgenic effect and it is regarded to be non-thermogenetic and non-sedative[5]
- Dydrogesterone is used in the treatment of infertility due to luteal phase insufficiency, dysmenorrhea, secondary amenorrhea, irregular menstrual cycles, premenstrual syndrome, threatened or recurrent miscarriage, abnormal uterine bleeding, pain in endometriosis and luteal phase support[7,8]
- It can improve pregnancy outcomes due to its favorable immunomodulatory effects[11-13]
- Dydrogesterone induces PIBF and nitric oxide production and it also has beneficial effects on lipid and lipoprotein profile in postmenopausal women[12,14,15,17]
- Compared with progesterone, dydrogesterone has a greater affinity for the PRs and can be used at lower oral doses owing to its better bioavailability and to the progestogenic activity of its metabolites[18]
- Dydrogesterone is associated with a reduction in the rate of spontaneous miscarriage in women clinically diagnosed with threatened miscarriage[26]
- Dydrogesterone appears to be an effective and well-tolerated treatment option for luteal phase support during IVF and it may replace MVP as the standard of care as it has the additional advantage of being more patient-friendly due to the oral route of administration.[31]

PRESCRIBING INFORMATION

Dydrogesterone Tablets IP

DUPHASTON®

Version: 6.0, dated 27th June 2018

Replaces: Version: 5.0, dated 7th March 2016

LABEL CLAIM

Each film coated tablet contains: Dydrogesterone IP 10 mg, Excipients q.s. Colour: Titanium dioxide IP.

INDICATION

Progesterone deficiencies

- Treatment of dysmenorrhoea
- Treatment of endometriosis
- Treatment of secondary amenorrhoea
- Treatment of irregular cycles
- Treatment of dysfunctional uterine bleeding
- Treatment of pre-menstrual syndrome
- Treatment of threatened miscarriage
- Treatment of habitual miscarriage
- Treatment of infertility due to luteal insufficiency
- Luteal support as part of an Assisted Reproductive Technology (ART) treatment
- Hormone replacement therapy.

DOSAGE AND ADMINISTRATION

Habitual miscarriage:

10 mg dydrogesterone twice daily until the twentieth week of pregnancy.

Threatened miscarriage:

An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30 mg per day until symptoms remit.

Infertility due to luteal insufficiency:

10 or 20 mg dydrogesterone daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles.

Luteal support as part of an Assisted Reproductive Technology (ART) treatment:

10 mg dydrogesterone three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed.

Endometriosis:

10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously.

Hormone replacement therapy:

- Continuous sequential therapy: An estrogen is dosed continuously and one tablet of 10 mg dydrogesterone is added for the last 14 days of every 28-day cycle, in a sequential manner.
- Cyclic therapy: When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12 -14 days of estrogen therapy.

Irregular cycles:

10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length.

Dysfunctional uterine bleeding:

When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days.

Dysmenorrhoea:

10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle.

Secondary amenorrhoea:

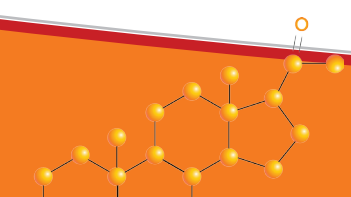
10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen.

Pre-menstrual syndrome:

10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length.

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients
- Known or suspected progestogen dependent neoplasms (e.g. meningioma)
- Undiagnosed vaginal bleeding. Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion /miscarriage
- Contraindications for the use of estrogens when used in combination with dydrogesterone.



WARNINGS & PRECAUTIONS

- Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified
- Breakthrough bleeding and spotting may occur during the first months of treatment
- If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy
- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised
- It should be taken into account that these conditions may recur or be aggravated during treatment with dydrogesterone and ceasing the treatment should be considered: Porphyria, Depression and Abnormal liver function values caused by acute or chronic liver disease.

PREGNANCY & LACTATION

Pregnancy & lactation

It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Dydrogesterone can be used during pregnancy if clearly indicated.

Breastfeeding

No data exist on excretion of dydrogesterone in mother's milk. Experiences with other progestogens indicate that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period.

Fertility

There is no evidence that dydrogesterone decreases fertility at therapeutic dose.

ADVERSE REACTIONS

The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/ headache, nausea, menstrual disorders and breast pain/ tenderness.

Undesirable effects in adolescent population

Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults.

Undesirable effects that is associated with an estrogen-progestogen treatment

- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Venous thromboembolism
- Myocardial infarction, coronary artery disease, ischemic stroke.

MANUFACTURED BY

Abbott India Limited

At: 16th Floor, Godrej BKC Plot C-68, 'G' Block, BKC, Near MCA Club, Bandra East, Mumbai- 400 051 India.

Based on information from: CCDS v6.0 dated 27 June 2018

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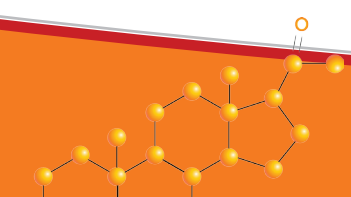

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Abbott India Limited, 3-4 Corporate Park, Sion-Trombay Road, Mumbai-400 071, India

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