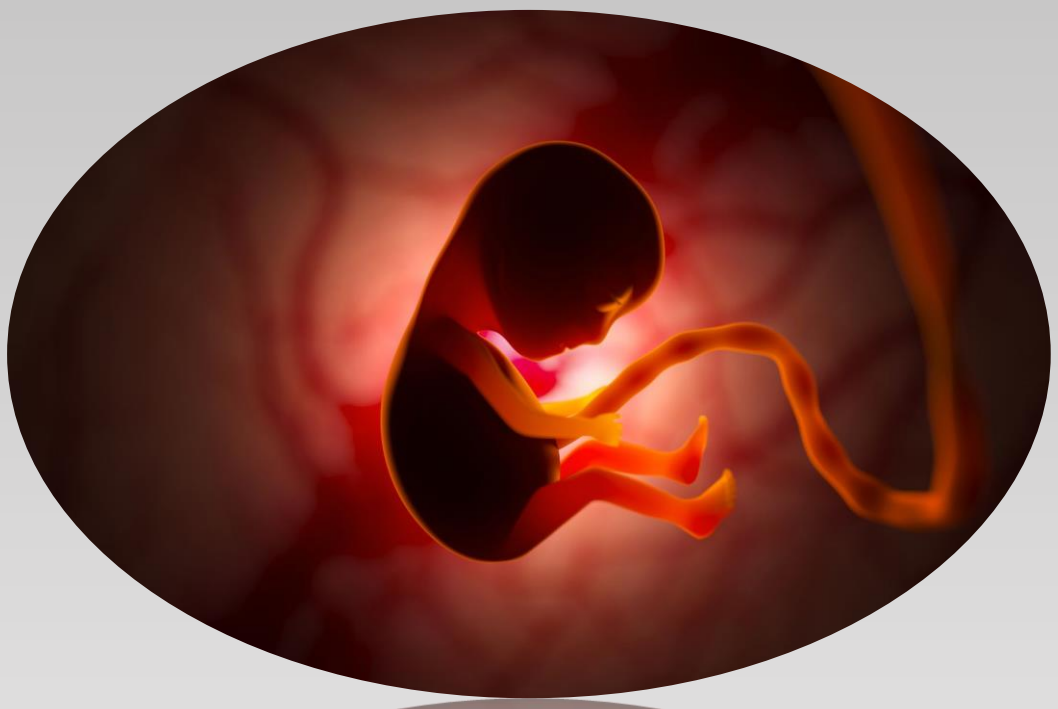
Role of Dydrogesterone in Recurrent Pregnancy Loss



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Background and Objective of the Survey

Dydrogesterone plays a significant role in the management of recurrent pregnancy loss (RPL), offering potential benefits in supporting pregnancy and reducing the risk of miscarriage in women with a history of recurrent pregnancy loss.

RPL is a challenging condition characterized by the occurrence of two or more consecutive pregnancy losses before 20 weeks of gestation. While the etiology of RPL is often multifactorial and complex, hormonal imbalances and inadequate luteal phase support have been implicated as potential contributing factors in some cases.

Dydrogesterone, a synthetic progestogen with progestational activity, is commonly used in the management of RPL to provide luteal phase support and promote endometrial receptivity for embryo implantation. Its unique pharmacological properties, including potent progestogenic effects with minimal androgenic, estrogenic, and glucocorticoid activity, make it an attractive option for women with RPL.

In clinical practice, dydrogesterone is typically initiated following ovulation or embryo transfer and continued until the end of the first trimester of pregnancy to support early gestation and reduce the risk of miscarriage. By providing adequate luteal phase support, dydrogesterone helps maintain the corpus luteum function, stabilize the endometrium, and create a favorable environment for embryonic development and implantation.

Several studies have evaluated the efficacy of dydrogesterone in RPL management, with promising results indicating a reduction in miscarriage rates and improved pregnancy outcomes in women receiving dydrogesterone supplementation. Meta-analyses and systematic reviews have also supported the use of dydrogesterone as an effective intervention for RPL, particularly in women with luteal phase defects or inadequate progesterone levels.

The objective of the survey is:

To evaluate the role of Dydrogesterone in recurrent pregnancy loss

Methodology of the Survey

A survey was conducted to evaluate the role of Dydrogesterone in recurrent pregnancy loss. A total of 125 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Dydrogesterone: background and pharmacology
- Is dydrogesterone effective for luteal phase support in fresh IVF cycles?
- Is oral administration preferred by the patient over vaginal administration?
- Is oral administration preferred by the physician over vaginal administration?
- Is oral dydrogesterone safe and well tolerated by the patient?
- Is dydrogesterone safe for the fetus?
- Clinical studies evaluating dydrogesterone in fresh cycle IVF
- Clinical studies evaluating dydrogesterone in frozen embryo transfer cycles
- Abstracts

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Dydrogesterone: background and pharmacology[1]

Dydrogesterone is a potent orally active progesterone receptor agonist that was developed in the 1950s and that has been widely used since the 1960s for menstrual disorders such as premenstrual syndrome, cycle irregularity, endometriosis, threatened miscarriage, and habitual miscarriage, and for postmenopausal hormone therapy. Unlike other members of the progestin family, dydrogesterone and its main active metabolite, 20α-hydroxydydrogesterone, do not have any clinically relevant agonistic or antagonistic activity on the androgen, estrogen, and glucocorticoid receptors and only mild antimineralocorticoid properties. Safety concerns owing to receptor cross-activation have precluded the use of the majority of the progestins in fertility treatment and pregnancy. Only bioidentical progesterone, 17-hydroxy-progesteronecaproate and dydrogesterone are considered to be sufficiently safe for the developing fetus.

Interestingly, dydrogesterone has only little effect on gonadotropin release and therefore hardly interferes with follicular growth and corpus luteum formation and maintenance. At clinically used doses (5–30 mg), ovulation is not suppressed in the human, although recently dydrogesterone (20 mg/d) has been used as an alternative to chlormadinone acetate for preventing premature LH surges in the context of controlled ovarian stimulation (COS).

In contrast to natural progesterone, dydrogesterone has good oral bioavailabilty (~28%). The half-life of dydrogesterone has been estimated to be 5–7 hours and the half-life of 20α-hydroxydydrogesterone to be 14–17 hours. Prereceptor regulation of action happens mostly by conversion of dydrogesterone to its biologically active 20α-hydroxymetabolite by aldoketo reductase 1C1, an enzyme that also converts progesterone to its less potent metabolite 20α-hydroxyprogesterone.

Dydrogesterone is currently not available in the United States; it was withdrawn from the market for commercial reasons. Likewise, the product was withdrawn from the United Kingdom market in 2008 and from the Australian market in 2011 for commercial reasons. For the United States, dydrogesterone was registered in 1961 and the license transferred over the years to several companies. In 1997, the current new drug application owner, Solvay, withdrew

the product because the registered indications were no longer commercially viable and/or there were potentially conflicting interest regarding other products of which Solvay was the license holder. For the United Kingdom and Australia, low sales of a comparatively cheap drug and the lack of new and commercially interesting indications motivated the withdrawal from the markets.

However, dydrogesterone is currently licensed for use in more than 100 countries globally, with more than 20 European countries having at least one label for use of dydrogesterone in pregnancy.

Dydrogesterone has long been used for exogenous support of endogenous progesterone production by the corpus luteum and placenta. Although definitive proof of luteal phase defect being an independent entity causing infertility has never been established, luteal phase defect is a well described iatrogenic phenomenon in the context of COS with multifollicular development and oocyte retrieval for in vitro fertilization (IVF). Studies comparing progestogen usage versus nil or placebo in COS IVF treatment cycles have reported that the use of progestogen is associated with an improvement in ongoing pregnancy or live birth rate. Accordingly, luteal phase support (LPS) with the use of progestogens is routinely performed in IVF treatment cycles.

Is dydrogesterone effective for luteal phase support in fresh IVF cycles? [1]

After many years of empirical use of dydrogesterone for LPS in IVF treatment, the first systematic comparisons of oral dydrogesterone versus vaginal progesterone originated from India. Prompted by poor patient acceptance of vaginal progesterone, Chakravarty et al. randomized 430 patients, 351 of which received luteal support with vaginal micronized progesterone (600 mg/d) and 79 with oral dydrogesterone (20 mg/d) after COS in a long GnRH-agonist protocol with 10,000 IU hCG triggering. Delivery rates were similar between the treatments (22.8% and 24.1% in the vaginal and oral group, respectively), which paved the way for further clinical investigations. By 2011, three randomized controlled trials (RCTs) encompassing 2,348 patients in total, comparing oral dydrogesterone with micronized vaginal progesterone for LPS in fresh IVF cycles were included in a Cochrane review (, which summarized that, “for the outcome clinical pregnancy, subgroup analysis of micronized progesterone versus synthetic progesterone showed a significant benefit from synthetic progesterone.” No conclusion could be drawn on ongoing pregnancy rate nor live birth rate,

because the larger studies did not report those outcomes. The conclusion of higher clinical pregnancy rate with the use of synthetic progesterone remained unaltered in an update of the Cochrane review in 2015. However, a substantial risk of bias of the included studies was criticized (e.g., unclear method of random sequence generation and concealment of allocation). By 2015, eight RCTs comparing oral dydrogesterone and either micronized vaginal progesterone (seven comparisons with a total n = 2,496) or vaginal gel (two comparisons with a total n = 1,735) were included in the latest systematic review and meta-analysis. Oral dydrogesterone was administered in daily doses of 20–40 mg, and 600–800 mg daily micronized progesterone or 8% vaginal gel (Crinone) was used in the control arms. It was found that the clinical pregnancy rate was higher in women treated with oral dydrogesterone compared with micronized vaginal progesterone (relative risk [RR] 1.19, 95% confidence interval [CI] 1.04–1.36; I^2 = 6%), an effect not seen in the comparison with vaginal gel. Despite the relatively large total sample size in the meta-analysis, risk of bias in the individual studies, clinical heterogeneity between the studies (for example in doses compared), incomplete outcome reporting (only clinical pregnancy rate was reported in most trials), and insufficient safety surveillance in nearly all of the trials still limited the external validity and clinical utility of the meta-analysis.

Of note, the study by Patki et al. comparing 30 mg/d oral dydrogesterone with 600 mg/d micronized vaginal progesterone in 675 randomized patients suggested superiority of oral dydrogesterone in terms of clinical pregnancy achievement (RR 1.39, 95% CI 1.13–1.72). Accordingly, that dose of dydrogesterone was chosen for further development, and in 2013 a company-sponsored phase III trial program was started, aiming to establish the efficacy and safety of daily 30 mg oral dydrogesterone compared with vaginal progesterone for LPS in IVF cycles with fresh embryo transfer. On completion, this program will have included more than 2,000 randomized study subjects in two large studies with complete assessment from start of treatment to childbirth and the child's health, respectively. Recently, the first of the two studies, LOTUS-I, was published. In this multinational, multicentric, randomized, double-blind, double-dummy clinical study, 1,031 patients undergoing IVF or intracytoplasmic sperm injection with fresh single or double embryo transfer after COS were randomized on the day of oocyte retrieval into one of the two treatment arms: The experimental group patients received oral dydrogesterone in 10 mg tablets (Abbott) with placebo intravaginal capsules (Catalent) three times daily, and the control group received micronized vaginal progesterone in 200 mg capsules (Utrogestan; Besins Healthcare) with oral placebo tablets (Abbott) starting

on the evening of the day of oocyte retrieval and discontinuing on a negative serum hCG test or at 12 gestational weeks. The study was designed and powered to show noninferiority of oral dydrogesterone for ongoing pregnancy likelihood at 12 gestational weeks. The double-dummy design mandated that each study subject received both oral tablets and vaginal capsules. Accordingly, the patient preference of one of these two routes of administration could not be studied. However, the double-dummy design allows assessing adverse events without the risk of differences in "nocebo" between groups (a self-fulfilling prophecy on purported side-effects of a given drug or route of administration).

The mean female age in the LOTUS I study was 32.5 years, mean body mass index was 23 kg/m^2, and ~43% of patients underwent single-embryo transfer. The LOTUS I trial firmly established that oral dydrogesterone is noninferior to micronized vaginal progesterone. The ongoing pregnancy rates were 37.6% and 33.1% in the oral and vaginal group treatment groups, respectively (difference +4.7% with dydrogesterone; 95% CI −1.2% to +10.6%). Similar results were observed for the live birth rate: 34.6% and 29.8% in the oral and vaginal treatment groups, respectively (difference +4.9% with dydrogesterone; 95% CI −0.8 to +10.7%). Of note, this single trial did not establish superiority at a statistical significant level owing to the design and sample size, which was still too small for a pregnancy rate difference of the magnitude of ≤5% to be detected with confidence. Conversely, noninferiority of 3 × 200 mg micronized vaginal progesterone against 3 × 10 mg oral dydrogesterone for LPS in a fresh IVF cycle has come under scrutiny with the LOTUS I trial results, because the 95% confidence interval of the difference in ongoing pregnancy at 12 weeks includes effect sizes (−1.2 to +10.6%) not in favor of vaginal progesterone, which most clinicians would not consider to be acceptable.

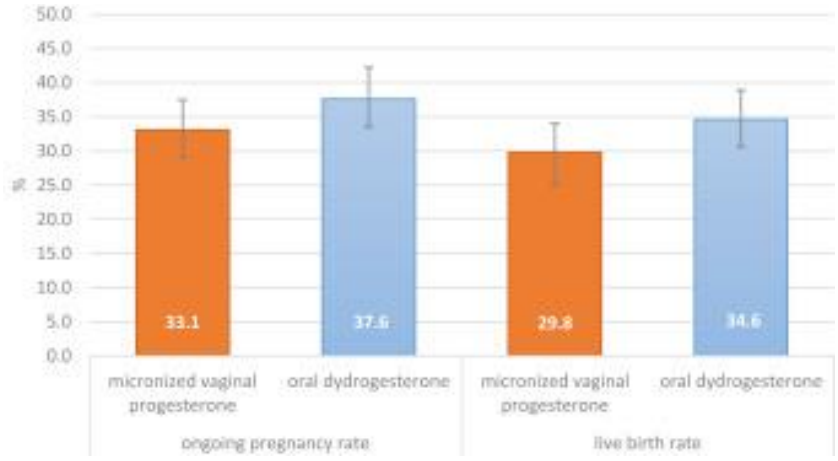

Figure 1. Ongoing pregnancy rates and live birth rates (with 95% confidence intervals) in the in the two groups (total n = 974) of the LOTUS I trial.

The comparator drug in the LOTUS I trial, Utrogestan, is not available in the United States. Utrogestan is a soft gelatin capsule consisting of 100 mg micronized progesterone in refined sunflower oil (previously peanut oil), soya lecithin, glycerol, titanium dioxide, and purified water. The two available preparations in the United States for vaginal administration of progesterone in the context of LPS in IVF are Endometrin and Crinone. Endometrin is an effervescent tablet consisting of, in essence, progesterone in starch (100 mg micronized progesterone in lactose monohydrate, polyvinylpyrrolidone (Povidone K29/32), adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate, pregelatinized maize starch, and colloidial silicone dioxide). Crinone is micronized progesterone administered as a gel, which is supposed to better adhere to the vaginal wall. One administration of Crinone 8% consists of 90 mg micronized progesterone in a gel of glycerol, paraffin-light liquid, hydrogenated palm oil glyceride, carbomer 974 P, polycarbophil, sorbic acid, sodium hydroxide, and purified water. Despite the use of different doses and administration regimen, differences in pregnancy rate between these vaginal preparations have never been documented. Beyond the evidence on oral dydrogesterone versus micronized vaginal progesterone cited above, dydrogesterone has been tested in two investigator-initiated randomized trials against progesterone in gel (Crinone 8%). No difference in ongoing pregnancy rates was found (RR 0.97, 95% CI 0.83–1.13), but the dose of oral dydrogesterone was only 20 mg/d in both trials. No randomized trial has compared vaginal Endometrin versus oral dydrogesterone. Likewise, no randomized trial has compared intramuscular progesterone versus oral dydrogesterone. Of note, intramuscular progesterone is still frequently used in the United States owing to concerns about the efficacy of vaginal progesterone. Because intramuscular progesterone is associated with significant side-effects, a randomized trial comparing oral dydrogesterone with intramuscular progesterone is warranted.

Is oral administration preferred by the patient over vaginal administration? [1]

Studies on the administration of, for example, vaginal versus oral misoprostol have consistently reported the oral route to be preferred by the majority of patients. Preference for oral administration may be even higher in the context of LPS, with a minimum intake duration of 10 days and often treatment extension into early pregnancy. Furthermore, patients exposed to once daily or three times daily administration of a vaginal progesterone prefer once daily application, because this was considered to be easier, more convenient, and less messy. It is

also noteworthy that in a recent phase III trial program comparing vaginal progesterone gel once daily with subcutaneous progesterone injection once daily for LPS, no difference in patient preference for one of the two administration routes could be seen, despite the fact that injectable drugs are usually less tolerated, especially when self-injected. In that trial, the incidence of vaginal irritation, inflammation, dryness, pruritus, discharge, or pain was 50.8% in patients on daily vaginal gel administration compared with 10.4% in patients on subcutaneous progesterone.

Chakravarty et al. reported, based on questionnaires handed out in the context of one of their randomized studies, that satisfaction of patients with the tolerability of oral dydrogesterone for LPS (2 × 10 mg) was significantly higher compared with micronized vaginal progesterone (3 × 200 mg). In another RCT on 831 patients undergoing IVF, patients were found to be significantly more often satisfied with oral dydrogesterone (2 × 10 mg) and more often significantly dissatisfied with once daily vaginal progesterone gel when ranking the drugs on scale from 1 to 5. No such difference was seen, however, in a recent study from Iran on 240 patients, in which total satisfaction and total dissatisfaction was equally distributed between 2 × 10 mg oral dydrogesterone and 2 × 400 mg vaginal micronized progesterone for LPS.

The above results illustrate that the preference for a route of administration in an individual patient is likely a function of personal habits and cultural circumstances. It has been suggested that patients may believe that they are receiving a “stronger” medicine when the administration is by injection or other uncomfortable route of administration and that such expectations may even influence the response to a drug. Although the latter is unlikely in the context of LPS, implicit judgments on a medication by an individual patient (efficacy beliefs), concerns about potential adverse reactions, and personal preferences should be taken into account to achieve good compliance and treatment adherence.

Is oral administration preferred by the physician over vaginal administration? [1]

Luteal phase support with the use of progesterone is usually started within the time interval between oocyte pick-up and embryo transfer. When the embryo transfer catheter passes through the cervical canal, there is a risk of introducing not only progesterone itself, but also excipients of tablets, suppositories, or gel into the uterine cavity. Furthermore, the supraphysiologic progesterone concentrations in the vagina may alter the local microbiome, which has become a recent focus of interest in the context of IVF.

Although a negative effect of drug excipients or high doses of progesterone on the endometrium, embryo, or the microbiome have never been documented, doctors usually take great care in cleaning the outer cervical os before the embryo transfer. A formal physician preference study has not been done, but an educated guess is that most doctors prefer a cleaner vagina (and therefore oral or injectable administration) when doing the embryo transfer or when performing a transvaginal scan at later stage.

Is oral dydrogesterone safe and well tolerated by the patient? [1]

Bioidentical orally administered progesterone has been associated with the formation of sedative metabolites due to a first pass effect in the liver. These metabolites act centrally, and side-effects of oral progesterone, such as fatigue, headache, and urinary frequency, in addition to safety concerns regarding intrahepatic cholestasis with oral progesterone intake, have prompted the development of vaginal preparations for LPS in IVF. The most important tolerability issue with vaginal progesterone is, however, discharge and irritation.

An objective assessment of the tolerability of dydrogesterone (20 mg/d) compared with vaginal micronized progesterone (600 mg/d) was done by Chakravarty et al.. Liver function tests were performed at baseline (before administration) and on the day of pregnancy test (e.g., after ~14 days of intake). The percentage of patients with abnormal liver function tests and the mean serum glutamate-pyruvate transaminase, bilirubin, and alkaline phosphatase levels were highly similar between the groups. In 10.5% of patients given micronized progesterone, vaginal discharge or irritation was confirmed, whereas 0% of dydrogesterone patients had those side-effects.

Tomic et al. reported that perineal irritation, vaginal bleeding, vaginal discharge, and interference with sexual activity was significantly higher in patients receiving vaginal progesterone gel compared with oral dydrogesterone. No difference was seen for dizziness, headache, nausea, breast tension, or bloating.

The most comprehensive and robust insight into the maternal safety and tolerability of oral dydrogesterone comes from the LOTUS I trial, in which doctors and patients were blinded and each patient was randomized to oral dydrogesterone or micronized vaginal progesterone and received a dummy medication with placebo. In addition, the patients were monitored for adverse events during later stages of pregnancy. Treatment emerging adverse events leading to

study termination were reported in 12.4% of subjects in the dydrogesterone group and in 16.0% of subjects in the micronized vaginal progesterone group. Liver enzyme analysis was normal in nearly all patients in both groups. Because most adverse events leading to study termination or discontinuation of the study drug were infrequent, events were grouped by organ system (e.g., gastrointestinal, nervous system, reproductive organ system, vascular system). No differences were identified, and no new safety or tolerability issues were found in this large study.

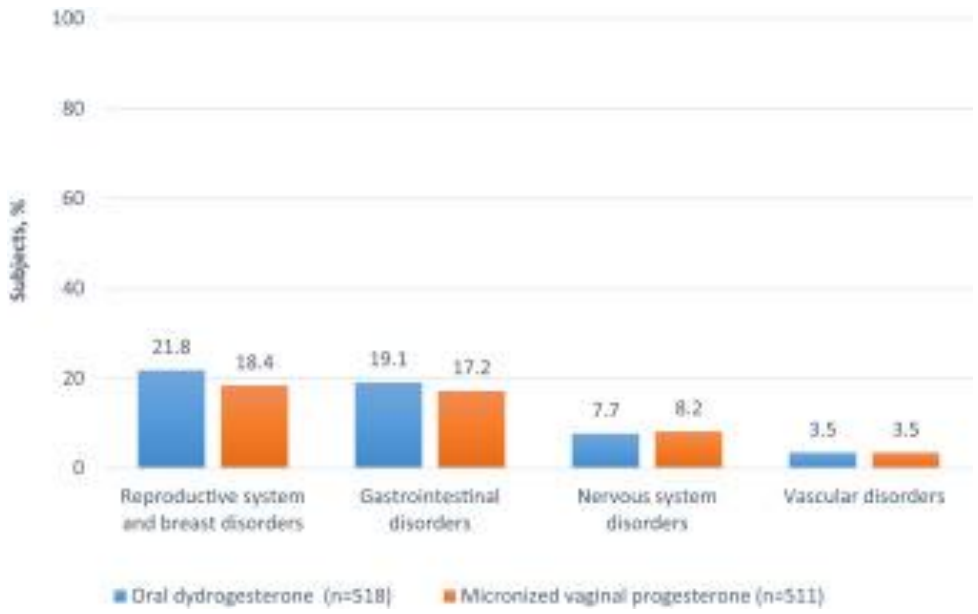

Figure 2. Proportion of female subjects reporting treatment emerging adverse events according to organ system in the two groups of the LOTUS I trial.

In summary, the use of oral dydrogesterone avoids the frequently reported and negatively perceived side effects of vaginal preparations, whereas no systemic tolerability difference from micronized vaginal progesterone has been identified in a large, double-blind, double-dummy randomized trial.

Is dydrogesterone safe for the fetus? [1]

Dydrogesterone has been on the market since the 1960s and is labeled for use in pregnancy (e.g., for recurrent miscarriage or threatening abortion) in numerous countries worldwide. From sales figures, it has been estimated that more than 8 million fetuses must have had in utero exposure to dydrogesterone during more than half a century of use on a global scale.

In view of this extensive use, a substantial fetal risk of dydrogesterone can be ruled out, although a low-level risk could be detected only via sophisticated and large observational studies.

A review and in-depth analysis of available pharmacovigilance data identified 28 cases of congenital defects with a potential link to dydrogesterone exposure in pregnancy recorded within the time span from 1977 to 2005.

Malformation rates associated with a drug can not be calculated from pharmacovigilance data, but the low number of reported cases (some of which occurred within controlled studies) in relation to the (estimated) number of pregnancies exposed makes a relevant teratogenic risk of dydrogesterone highly unlikely. Moreover, the types of defects potentially associated with dydrogesterone in the pharmacovigilance data were very diverse, with no evidence of a pattern of abnormalities.

In the LOTUS I trial, child health was recorded at birth for the total maternal population and 6 months after birth in a subset of 216 patients who had been treated in Russia. Overall, 213 and 158 children were recorded in the oral dydrogesterone and vaginal progesterone group, respectively. The incidences of congenital, familial, and genetic disorders were <2% in both treatment groups. No difference in the incidence of congenital malformations was found, and no distinct pattern of defects with the use dydrogesterone or progesterone was observed.

Further safety data stem from RCTs on dydrogesterone use in threatened miscarriage and recurrent miscarriage. None of those studies revealed a safety concern with dydrogesterone use.

In 2015, a retrospective case-control study compared exposure to dydrogesterone in pregnancy in 202 children born with congenital heart disease and a control group of 200 healthy children born from 2010 to 2013 in the Gaza strip of Palestine.

Dydrogesterone exposure was defined as any reported use (by recall) in the first trimester of pregnancy. A higher rate of dydrogesterone intake was found in mothers of children with a heart defect (38%) compared with control children (18%), and the authors concluded that there was a positive association between dydrogesterone use during early pregnancy and congenital heart disease in the offspring (adjusted odds ratio 2.71, 95% CI 1.54–4.24; P<.001). However, this study violated numerous basic principles of epidemiologic research. First, all comparisons should have been made within the same study base, that is, women who have had an indication

for dydrogesterone and who did or did not receive that drug. Second, because dydrogesterone is often prescribed for miscarriage prevention, all women should have had a similar risk background; the difference in maternal population leads to the issue of confounding: There is evidence from the literature that previous miscarriages are an important and strong risk factor for congenital heart defects. Third, the authors did not confirm exposure (at least retrospectively based on medical records) but instead relied on recollection of the mothers. However, mothers are likely to recollect any event in pregnancy better if their child has an abnormality. Finally, different heart defects were pooled into one group and socioeconomic status was ignored, as were comorbidities. In summary, a causal relationship of dydrogesterone and heart defects can not be inferred from this study.

Congenital heart defects are common, with an estimated incidence of 1%. A study verifying or refuting the hypothesis of a threefold increased risk of a heart defect in offspring exposed to dydrogesterone would require >3,000 infants to be studied in a 1:1 randomized trial. With a live birth rate of 30% in patients undergoing IVF, a two-armed study on women receiving dydrogesterone or a control drug for LPS in IVF treatment would therefore require a total sample size of ≥10,000 patients (alpha error <5%, beta error <20%). It is unlikely that a study of such dimension will soon be performed, and physicians therefore will have to rely on the available pharmacovigilance data. Of note, larger-size randomized studies assessing the risk of bioidentical progesterone have not been conducted, despite the fact that a theoretic risk of bioidentical progesterone in supraphysiologic doses can not be ruled out.

Clinical Studies Evaluating Dydrogesterone in Fresh Cycle IVF[2]

Several small-scale clinical studies have shown that oral dydrogesterone is at least as efficacious as micronized vaginal progesterone in supporting pregnancy following fresh embryo transfer. These findings revived the interest in oral dydrogesterone for LPS and paved the way for large Phase III prospective RCTs (Lotus I and Lotus II studies), which led to the recent approval of oral dydrogesterone for LPS in IVF–ART.

In particular, Lotus I was an international Phase III non-inferiority RCT including 1,034 patients undergoing IVF and fresh embryo transfer, which showed that dydrogesterone 30 mg (10 mg three times daily) resulted in comparable ongoing pregnancy rates (pregnancy rates at 12 weeks of gestation of 37.6 and 33.1% in the oral dydrogesterone and micronized vaginal P group, respectively) compared to vaginal micronized P 600 mg (200 mg three times daily).

Similarly, Lotus II RCT compared oral dydrogesterone 30 mg (10 mg three times daily) with 8% micronized vaginal P gel (90 mg once daily) and demonstrated non-inferiority, with ongoing pregnancy rates at 12 weeks' gestation of 38.7% in the oral dydrogesterone group and 35.0% in the micronized vaginal progesterone gel group. The main conclusion of the two RCTs was that oral dydrogesterone is safe (no evidence for an increased risk for fetal malformation), well-tolerated and as efficient as vaginal P.

Clinical Studies Evaluating Dydrogesterone in Frozen Embryo Transfer Cycles[2]

Frozen-thawed embryo transfer (FET) has become an increasingly important part of IVF treatment, with large clinical trials and meta-analyses demonstrating similar live birth rates to those associated with fresh embryo transfer. To date, several methods of endometrial preparation for FET have been developed, with hormone replacement therapy (HRT)-FET cycles being the most commonly used, in view of the reduced need for treatment monitoring and easier scheduling. In HRT-FET cycles estrogen and progesterone are administered consecutively, in order to mimic the endocrine conditions of the endometrium of a normal menstrual cycle. However, from an physiological point of view, LPS in HRT-FET is completely different compared to LPS in a fresh IVF cycle due to the lack of ovulation and absence of endogenous corpora lutea, suggesting that transformation of the endometrium into a receptive state for the implanting embryo is completely dependent on exogenous P supplementation.

While there is robust evidence demonstrating the efficacy of oral dydrogesterone for LPS in fresh IVF cycles as mentioned above, very few small studies using inconsistent doses have evaluated the role of dydrogesterone in HRT-FET cycles. In the only RCT performed up to date, Zarei et al. reported lower pregnancy rates in the oral dydrogesterone group compared to the micronized vaginal P group, using doses of 20 and 800 mg, respectively. However, the lack of data with regard to the optimal dosing of oral dydrogesterone in FET-HRT, highlights the need for further studies. In view of the advancing understanding of the impact of an absent corpus luteum in FET-HRT cycles and the associated elevated risk for PE, dydrogesterone with its potential immunomodulatory effects represents an interesting research track. Of great importance will be the development of a clinically applicable dose monitoring test for dydrogesterone and/or its metabolites, as an optimal LPS presumably lies in its individualization.

Table 1. Overview of evidence of dydrogesterone use in HRT-FET cycles.

Study	***N***	**Study design**	**LPS in HRT-FET**	**Embryo stage**	**Outcome**
Zarei et al.	400	RCT	400 mg MVP 2x/d vs. 10 mg DYD 2x/d vs. 10 mg DYD 2x/d + 0.1 mg GnRHa vs. 10 mg DYD 2x/day + 1500 IU hCG	Cleavage stage	CPR 20, 9, 25, and 17% (p = 0.03) OPR 18, 9, 3, and 17% (p = 0.07) MR 18.1, 35.7, 14.8, and 19.1% (p = 0.84)
Alahmad et al.	314	Retrospective	MVP 600 mg/day of 90 mg vs. DYD 10 mg 3x/day	2PN	Cumulative CPR Difference: 1.4%, 95% CI: (−9.4 to 12.6), p = 0.80 CPR of first FET Difference: −3.2%, 95%CI: (−12.8 to 7.4), p = 0.54
Guo et al.	529	Retrospective	DYD 10 mg 4x/day vs. IM P4 60 mg/day	Cleavage stage/blastocyst	CPR IR MR EPR OPR DR no significant difference

Rashidi et al.	180	Pilot RCT	IM P4 50 mg 2x/d vs. DYD 20 mg 2x/d vs. MVP 400 mg 2x/d	95% cleavage stage5% blastcyst	CPR MR LBR no significant difference

LPS, luteal phase support; HRT, hormone replacement therapy; FET, frozen embryo transfer; RCT, randomized controlled trial; MVP, micronized vaginal progesterone, DYD, dydrogesterone; GnRHa, gonadotrophin releasing hormone agonist; hCG, human chorionic gonadotrophin; IM P4, intramuscular progesterone; PN, pronuclei; CPR, clinical pregnancy rate; OPR, ongoing pregnancy rate; MR, miscarriage rate; IR, implantation rate; EPR, ectopic pregnancy rate; DR, delivery rate; LBR, life birth rate.

Abstracts

Live birth rates and safety profile using dydrogesterone for luteal phase support in assisted reproductive techniques[3]

Abstract

Introduction: Assisted reproductive techniques (ARTs) result in a deficient luteal phase, requiring the administration of intramuscular, intravaginal or oral exogenous progesterone. Dydrogesterone, an oral retroprogesterone with good bioavailability, has been used in assisted reproductive cycles with outcomes that are comparable to those of vaginal or intramuscular progesterone. However, there are limited reviews on its use for luteal phase support in ARTs, in terms of pregnancy outcomes and associated fetal anomalies. This study aimed to review the live birth rates and associated fetal anomalies of women who were given dydrogesterone for luteal phase support in assisted reproductive cycles at a tertiary hospital in Singapore.

Methods: This retrospective descriptive study included 1,050 women who underwent in vitro fertilisation/intracytoplasmic sperm injection at the Centre for Assisted Reproduction of Singapore General Hospital between 2000 and 2011. The women were given dydrogesterone for luteal phase support. The main outcome measures were rates of pregnancy, live birth, miscarriage and fetal anomalies.

Results: The pregnancy and live birth rates were 34.7% and 27.7%, respectively. Among those who achieved pregnancy, 17.0% miscarried, 0.8% had ectopic pregnancies and 0.3% had molar pregnancies. Fetal anomalies were detected in 1.9% of pregnancies, all of which were terminated by choice.

Conclusion: Since the outcomes of dydrogesterone are comparable to those of intramuscular and vaginal progesterone, it is a reasonable option to provide luteal phase support for women who are uncomfortable with injections or vaginal insertions. Randomised controlled studies are needed to determine the optimal dosage of dydrogesterone for luteal phase support in ARTs.

Oral dydrogesterone vs. vaginal progesterone capsules for luteal-phase support in women undergoing embryo transfer: a systematic review and meta-analysis[4]

Abstract

Objective: To identify, appraise, and summarize the evidence from randomized controlled trials (RCTs) comparing oral dydrogesterone to vaginal progesterone capsules for luteal-phase support (LPS) in women offered fresh or frozen embryo transfers following in vitro fertilization.

Methods: Two independent authors screened the literature for papers based on titles and abstracts, then selected the studies, extracted data, and assessed the risk of bias. Dydrogesterone and progesterone were compared based on risk ratios (RR) and the precision of the estimates was assessed through the 95% confidence interval (CI).

Results: An electronic search performed on June 7, 2017 retrieved 376 records, nine of which were papers deemed eligible and included in this systematic review and quantitative analysis. Good quality evidence indicates that oral dydrogesterone provided at least similar results than vaginal progesterone capsules on live birth/ongoing pregnancy (RR=1.08, 95%CI=0.92-1.26, I2=29%, 8 RCTs, 3,386 women) and clinical pregnancy rates (RR 1.10, 95% CI 0.95 to 1.27; I2=43%; 9 RCTs; 4,061 women). Additionally, moderate quality evidence suggests there is no relevant difference on miscarriage rates (RR=0.92, 95%CI=0.68-1.26, I2=6%, 8 RCTs, 988 clinical pregnancies; the quality of the evidence was downgraded because of imprecision).

Conclusions: Good quality evidence from RCTs suggest that oral dydrogesterone provides at least similar reproductive outcomes than vaginal progesterone capsules when used for LPS in women undergoing embryo transfers. Dydrogesterone is a reasonable option and the choice of either of the medications should be based on cost and side effects.

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[5]

Abstract

Study question: Is oral dydrogesterone 30 mg daily (10 mg three times daily [TID]) non-inferior to micronized vaginal progesterone (MVP) 600 mg daily (200 mg TID) for luteal support in in vitro fertilization (IVF), assessed by the presence of fetal heartbeats determined by transvaginal ultrasound at 12 weeks of gestation?

Summary answer: Non-inferiority of oral dydrogesterone versus MVP was demonstrated at 12 weeks of gestation, with a difference in pregnancy rate and an associated confidence interval (CI) that were both within the non-inferiority margin.

What is known already: MVP is routinely used in most clinics for luteal support in IVF, but it is associated with side effects, such as vaginal irritation and discharge, as well as poor patient acceptance. Dydrogesterone may be an alternative treatment due to its patient-friendly oral administration.

Study design, size, duration: Lotus I was an international Phase III randomized controlled trial, performed across 38 sites, from August 2013 to March 2016. Subjects were premenopausal women (>18 to <42 years of age; body mass index (BMI) ≥18 to ≤30 kg/m2) with a documented history of infertility who were planning to undergo IVF. A centralized electronic system was used for randomization, and the study investigators, sponsor's study team, and subjects remained blinded throughout the study.

Participants/materials, setting, methods: In total, 1031 subjects were randomized to receive either oral dydrogesterone (n = 520) or MVP (n = 511). Luteal support was started on the day of oocyte retrieval and continued until 12 weeks of gestation (Week 10), if a positive pregnancy test was obtained at 2 weeks after embryo transfer.

Main results and the role of chance: In the full analysis set (FAS), 497 and 477 subjects in the oral dydrogesterone and MVP groups, respectively, had an embryo transfer. Non-inferiority of oral dydrogesterone was demonstrated, with pregnancy rates at 12 weeks of gestation of 37.6% and 33.1% in the oral dydrogesterone and MVP treatment groups, respectively (difference 4.7%; 95% CI: -1.2-10.6%). Live birth rates of 34.6% (172 mothers with 213 newborns) and 29.8% (142 mothers with 158 newborns) were obtained in the dydrogesterone

and MVP groups, respectively (difference 4.9%; 95% CI: -0.8-10.7%). Oral dydrogesterone was well tolerated and had a similar safety profile to MVP.

Limitations, reasons for caution: The analysis of the results was powered to consider the clinical pregnancy rate, but the live birth rate may be of greater clinical interest. Conclusions relating to the differences between treatments in live birth rate, observed in this study, should therefore be made with caution.

Wider implications of the findings: 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, as well as it being a well tolerated and efficacious treatment.

Live birth rates and safety profile using dydrogesterone for luteal phase support in assisted reproductive techniques[6]

Abstract

Introduction: Assisted reproductive techniques (ARTs) result in a deficient luteal phase, requiring the administration of intramuscular, intravaginal or oral exogenous progesterone. Dydrogesterone, an oral retroprogesterone with good bioavailability, has been used in assisted reproductive cycles with outcomes that are comparable to those of vaginal or intramuscular progesterone. However, there are limited reviews on its use for luteal phase support in ARTs, in terms of pregnancy outcomes and associated fetal anomalies. This study aimed to review the live birth rates and associated fetal anomalies of women who were given dydrogesterone for luteal phase support in assisted reproductive cycles at a tertiary hospital in Singapore.

Methods: This retrospective descriptive study included 1,050 women who underwent in vitro fertilisation/intracytoplasmic sperm injection at the Centre for Assisted Reproduction of Singapore General Hospital between 2000 and 2011. The women were given dydrogesterone for luteal phase support. The main outcome measures were rates of pregnancy, live birth, miscarriage and fetal anomalies.

Results: The pregnancy and live birth rates were 34.7% and 27.7%, respectively. Among those who achieved pregnancy, 17.0% miscarried, 0.8% had ectopic pregnancies and 0.3% had molar pregnancies. Fetal anomalies were detected in 1.9% of pregnancies, all of which were terminated by choice.

Conclusion: Since the outcomes of dydrogesterone are comparable to those of intramuscular and vaginal progesterone, it is a reasonable option to provide luteal phase support for women who are uncomfortable with injections or vaginal insertions. Randomised controlled studies are needed to determine the optimal dosage of dydrogesterone for luteal phase support in ARTs.

Dydrogesterone as an oral alternative to vaginal progesterone for IVF luteal phase support: A systematic review and individual participant data meta-analysis[7]

Abstract

The aim of this systematic review and meta-analysis was to conduct a comprehensive assessment of the evidence on the efficacy and safety of oral dydrogesterone versus micronized vaginal progesterone (MVP) for luteal phase support. Embase and MEDLINE were searched for studies that evaluated the effect of luteal phase support with daily administration of oral dydrogesterone (20 to 40 mg) versus MVP capsules (600 to 800 mg) or gel (90 mg) on pregnancy or live birth rates in women undergoing fresh-cycle IVF (protocol registered at PROSPERO [CRD42018105949]). Individual participant data (IPD) were extracted for the primary analysis where available and aggregate data were extracted for the secondary analysis. Nine studies were eligible for inclusion; two studies had suitable IPD (full analysis sample: n = 1957). In the meta-analysis of IPD, oral dydrogesterone was associated with a significantly higher chance of ongoing pregnancy at 12 weeks of gestation (odds ratio [OR], 1.32; 95% confidence interval [CI], 1.08 to 1.61; P = 0.0075) and live birth (OR, 1.28; 95% CI, 1.04 to 1.57; P = 0.0214) compared to MVP. A meta-analysis combining IPD and aggregate data for all nine studies also demonstrated a statistically significant difference between oral dydrogesterone and MVP (pregnancy: OR, 1.16; 95% CI, 1.01 to 1.34; P = 0.04; live birth: OR, 1.19; 95% CI, 1.03 to 1.38; P = 0.02). Safety parameters were similar between the two groups. Collectively, this study indicates that a higher pregnancy rate and live birth rate may be obtained in women receiving oral dydrogesterone versus MVP for luteal phase support.

Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis[8]

Abstract

Background: This study aimed to explore the clinical efficacy of dydrogesterone in treating recurrent spontaneous abortion (RSA), analyze the influence of dydrogesterone on cellular immune factors, and provide evidence for clinical medication.

Methods: We used the China National Knowledge Infrastructure (CNKI) platform, Wanfang Data resource, PubMed, Web of Science, and Embase database to conduct a literature search to screen clinical studies published between 2005 and 2021 concerning dydrogesterone treatment for RSA. Stata 16.0 was used for meta-analysis and sensitivity analysis, and Begg's funnel chart was used to test publication bias.

Results: Only 13 studies, which included a total of 2,454 RSA patients, met the study inclusion criteria. The experimental group was treated with dydrogesterone, and the control group was treated with progesterone, human chorionic gonadotropin (hCG), placebo, or active immunization. Meta-analysis showed that the pregnancy success rate of the experimental group was higher than the control group, and the adverse reaction rate was lower than the control group. In addition, subgroup analysis also revealed that the experimental group had a higher pregnancy success rate than the control group and a lower adverse reaction rate. Levels of progesterone and hCG in the experimental group were dramatically higher than the control group after treatment. The experimental group also had higher levels of interleukin 4 (IL-4) and interleukin 10 (IL-10) than the control group, while levels of interferon-gamma (IFN-γ) were lower.

Discussion: Dydrogesterone, a safe and effective synthetic progesterone drug, had a significant clinical effect on RSA and effectively improved hormone levels and related cellular immune factors in RSA patients.

Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion[9]

Abstract

Background: Threatened abortion is a relatively common complication during pregnancy. Inadequate production of endogenous progesterone is implicated as a risk factor for miscarriages. Thus, supplementation of external progesterone can be used as a preventive strategy in these women. Dydrogesterone a stereoisomer of progesterone has a good safety and tolerability profile and is known to effectively prevent pregnancy loss in women with threatened miscarriage, however, real-world data safety and effectiveness analysis of dydrogesterone in Indian patients was lacking. Therefore, this real-world retrospective analysis of the case reports was done to evaluate the safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the treatment of women with threatened abortion.

Methods: Data was collected from 194 obstetricians and gynaecologists in India, on the use of oral dydrogesterone in women presenting with threatened abortion in the first trimester of pregnancy.

Results: Completed case report forms of patients who met the eligibility criteria (n = 617) were considered for the analysis. The main presenting symptom was vaginal bleeding/spotting with an additional symptom of abdominal cramp/pelvic pain/low back pain in 364 (69.07%) patients. Miscarriage was reported in 45 (7.29%) patients and 23 (3.98%) patients needed surgical intervention before 20 weeks of gestation with dydrogesterone treatment. The median time for relief of symptoms from the start of dydrogesterone tablets was 3.32 days for low back pain, 3.9 days for abdominal pain, and 4.37 days for the establishment of hemostasis. Treatment with dydrogesterone was found to be well-tolerated and adverse events were reported in 3.72% of the patients.

Conclusions: This retrospective analysis suggests that dydrogesterone is safe and effective in reducing the incidence of pregnancy loss in women with threatened abortion.

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8. Guo H, Lu Q. Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis. *Ann Palliat Med*. 2021;10(10):10971-10985.
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Survey Form

1) How frequently do you encounter cases of Recurrent Pregnancy Loss (RPL) in your practice?

<5%

5-10%

11-15%

15-20%

21-30%

>30%

2) Which cases of RPL are commonly seen in your practice?

Primary Pregnancy Loss

Secondary Pregnancy Loss

3) What are the common risk factors for RPL?

Female age >40 yrs

Endometriosis

Smoking

Excessive Alcohol consumption

4) Which of the following is your most preferred type of progestogen inrecurrent pregnancy loss?

Oral micronized progesterone

Vaginal micronized progesterone

IM/SC progesterone

Dydrogesterone

5) Do you use dydrogesterone in Recurrent Pregnancy Loss (RPL)?

Yes

No

6) How do you use dydrogesterone in your patients with RPL?

As a monotherapy

In combination with oral/vaginal micronized progesterone

7) What is the preferred dose of dydrogesterone in RPL?

10 mg BID from the onset of bleeding until 1 week after bleeding has stopped

10 mg BID from the onset of bleeding until the 16th week of pregnancy

40 mg loading dose followed by 20–30 mg/day until 7 days after bleeding stops

40 mg immediately, followed by 10 mg every 8 h until symptoms abate; then continue oral dydrogesterone for 1 to 2 weeks

8) Do you monitor serum P levels after administration of dydrogesterone in RPL?

Yes

No

Sometimes

9) In what % of your patients do you use dydrogesterone in RPL?

1-10%

11-20%

21-30%

31-40%

41-50%

>50%

10) According to you, which of the following are unique features ofdydrogesterone over conventional progestogens?

Oral route of administration

Lower affinity for androgens and glucocorticoid receptors

Better bioavailability compared to oral and vaginal micronized progesterone

Greater affinity for P receptors

11) What are the important benefits of using dydrogesterone in RPL?

Higher pregnancy rate

Lower adverse effects

Improved hormonal level

Immune regulation of the maternal-fetal interface

All of the above

12) In the past, have you used Dydroeva in your practice?

Yes

No

13) How would you rate your experience (in terms of efficacy) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best)?

1

2

3

4

5

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10

14) How would you rate your experience (in terms of safety) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best)?

1

2

3

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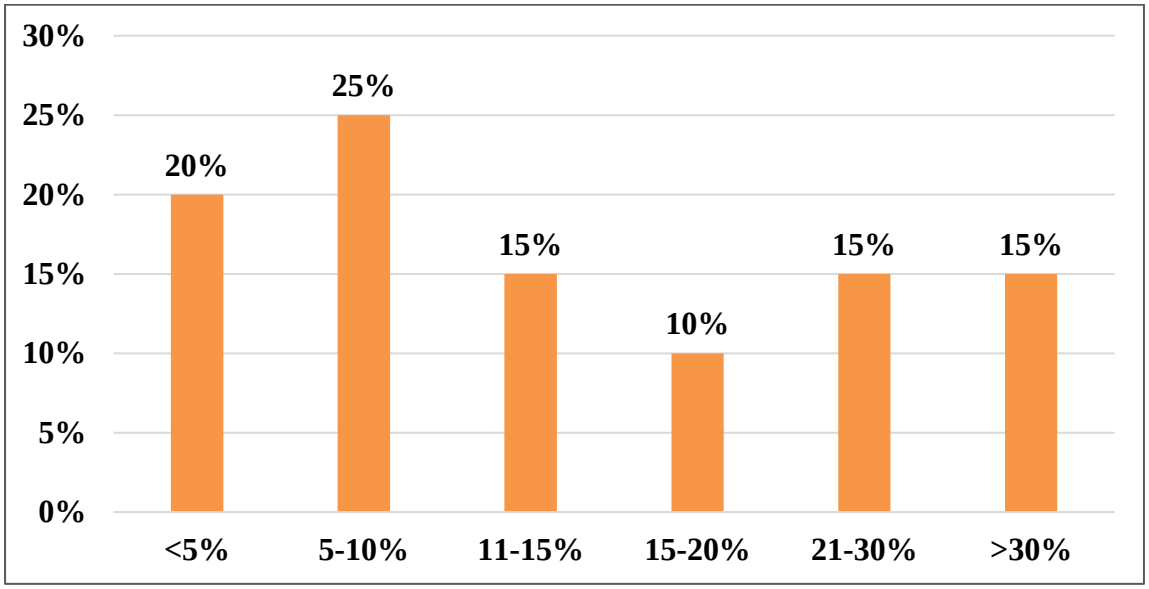
9

10

Survey Findings

1) How frequently do you encounter cases of Recurrent Pregnancy Loss (RPL) in your practice?

a. <5%
b. 5-10%
c. 11-15%
d. 15-20%
e. 21-30%
f. >30%

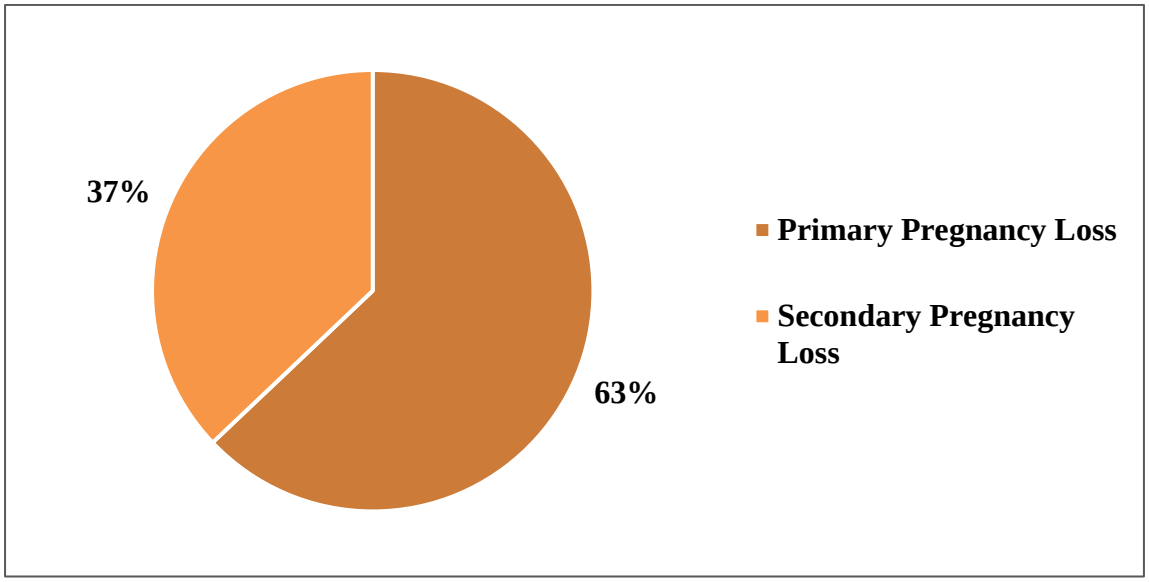


25% of doctors encounter 5 – 10% cases of Recurrent Pregnancy Loss (RPL) in your practice.

2) Which cases of RPL are commonly seen in your practice?

a. Primary Pregnancy Loss

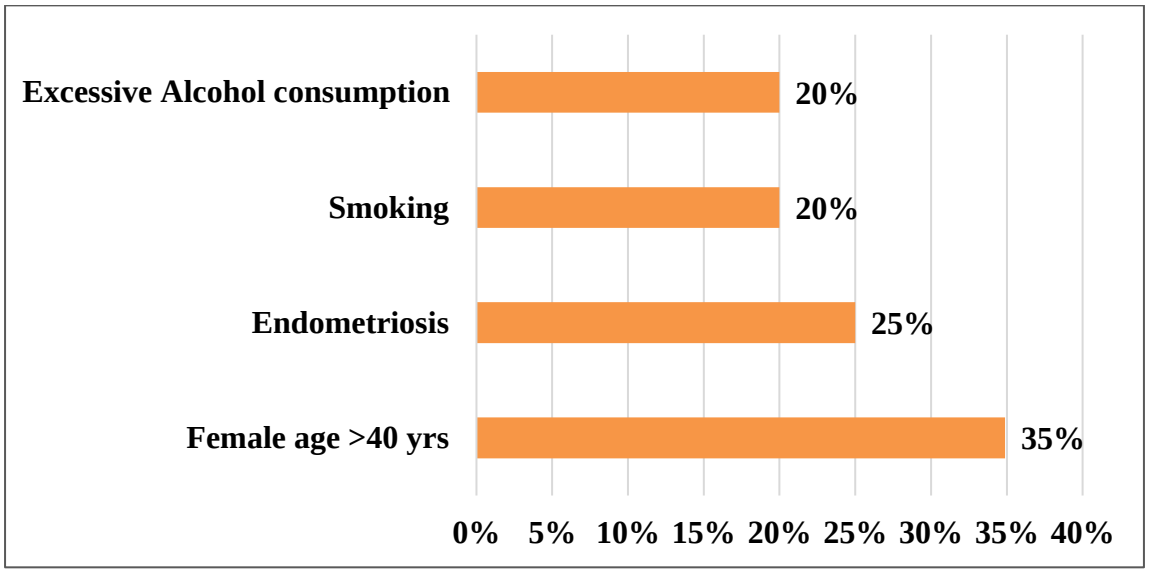
b. Secondary Pregnancy Loss



According to majority of doctors, 63%, primary pregnancy loss cases of RPL are commonly seen in their practice.

3) What are the common risk factors for RPL?

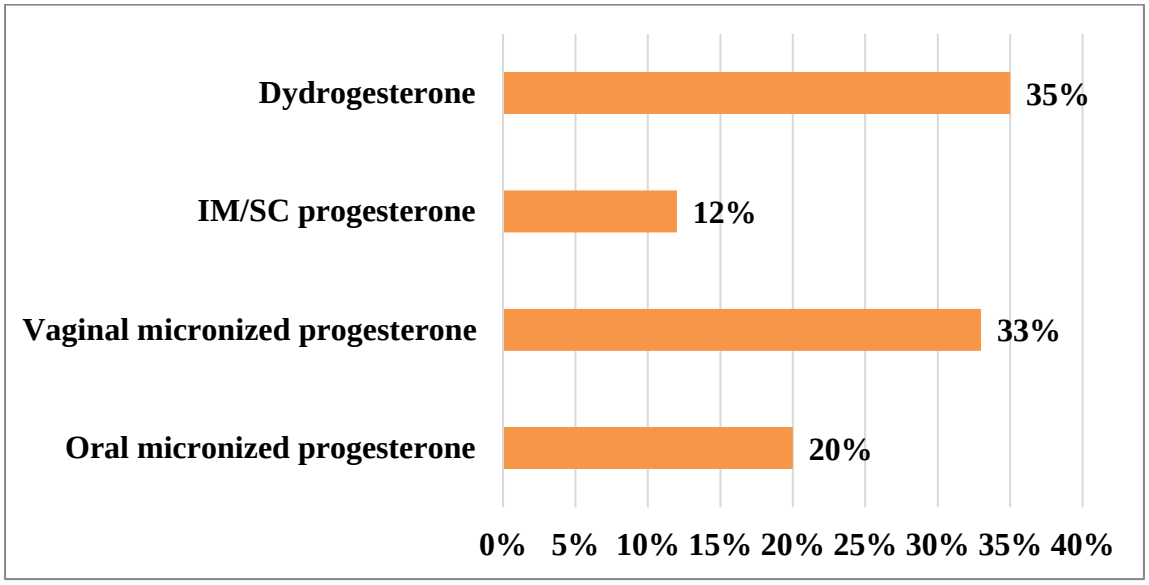
a. Female age >40 yrs
b. Endometriosis
c. Smoking
d. Excessive Alcohol consumption



As per 35% of doctors, the common risk factors for RPL is female age >40 years.

4) Which of the following is your most preferred type of progestogen in recurrent pregnancy loss?

a. Oral micronized progesterone
b. Vaginal micronized progesterone
c. IM/SC progesterone
d. Dydrogesterone

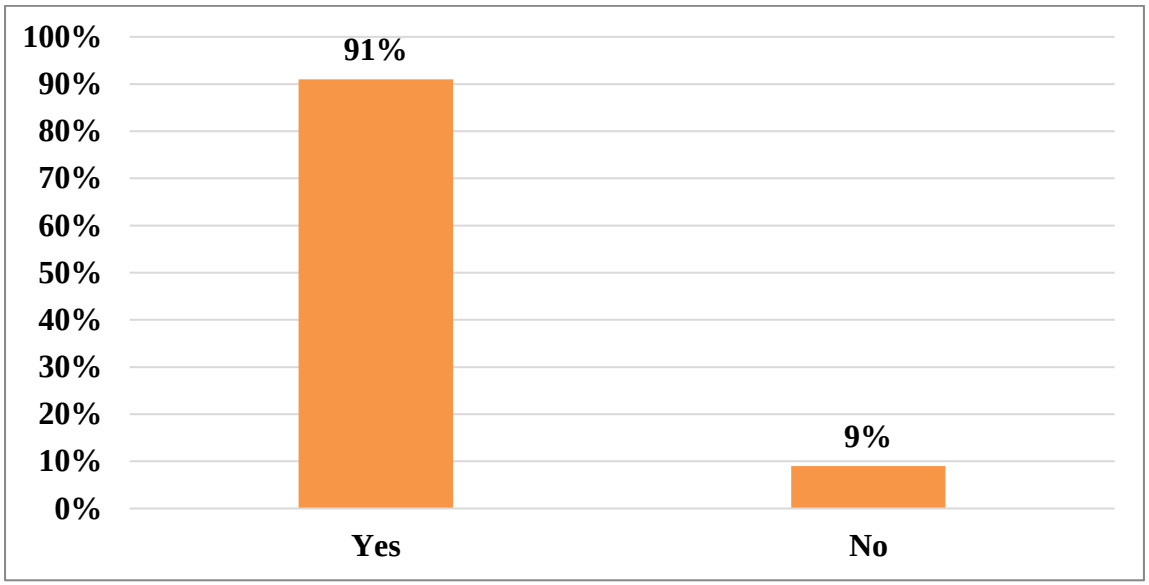


According to 35% of doctors, most preferred type of progestogen in recurrent pregnancy loss is Dydrogesterone.

5) Do you use dydrogesterone in Recurrent Pregnancy Loss (RPL)?

a. Yes

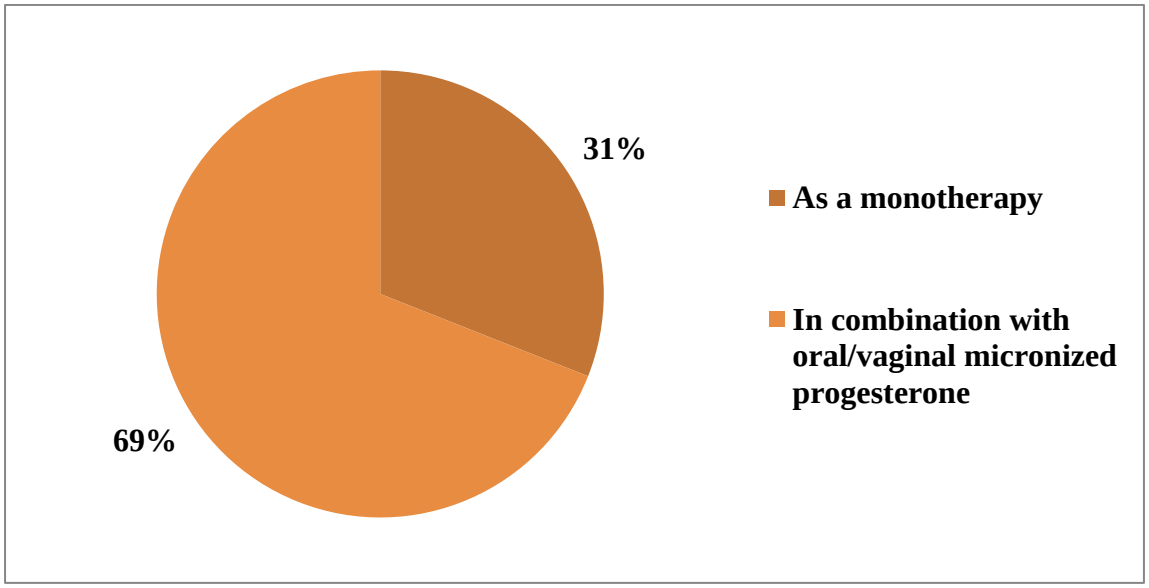
b. No



Majority of doctors, 91%, use dydrogesterone in Recurrent Pregnancy Loss (RPL).

6) How do you use dydrogesterone in your patients with RPL?

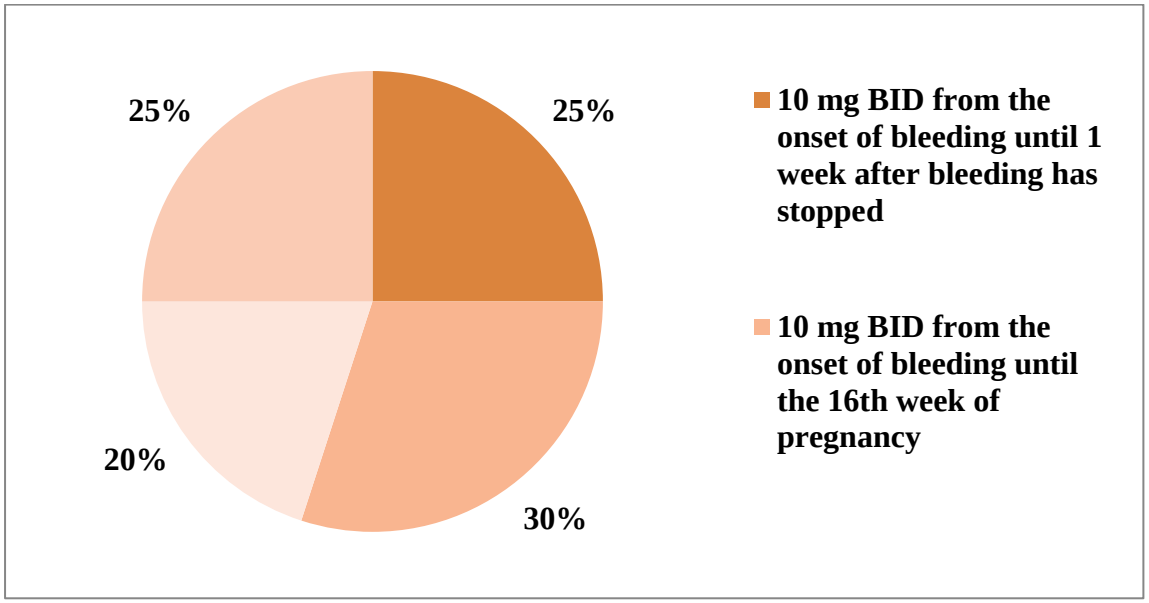
a. As a monotherapy
b. In combination with oral/vaginal micronized progesterone



Majority of doctors, 69%, use dydrogesteron in combination with oral/vaginal micronized progesterone in their patients with RPL.

7) What is the preferred dose of dydrogesterone in RPL?

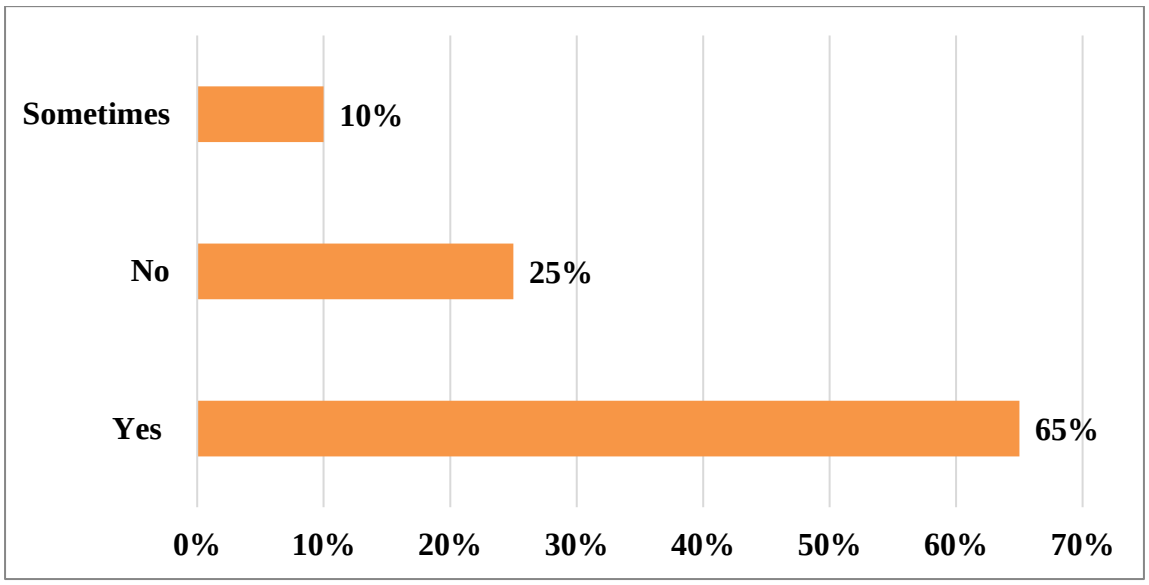
a. 10 mg BID from the onset of bleeding until 1 week after bleeding has stopped
b. 10 mg BID from the onset of bleeding until the 16th week of pregnancy
c. 40 mg loading dose followed by 20–30 mg/day until 7 days after bleeding stops
d. 40 mg immediately, followed by 10 mg every 8 h until symptoms abate; then continue oral dydrogesterone for 1 to 2 weeks



As per 30% of doctors, the preferred dose of dydrogesterone in RPL is 10 mg BID from the onset of bleeding until the 16th week of pregnancy.

8) Do you monitor serum P levels after administration of dydrogesterone in RPL?

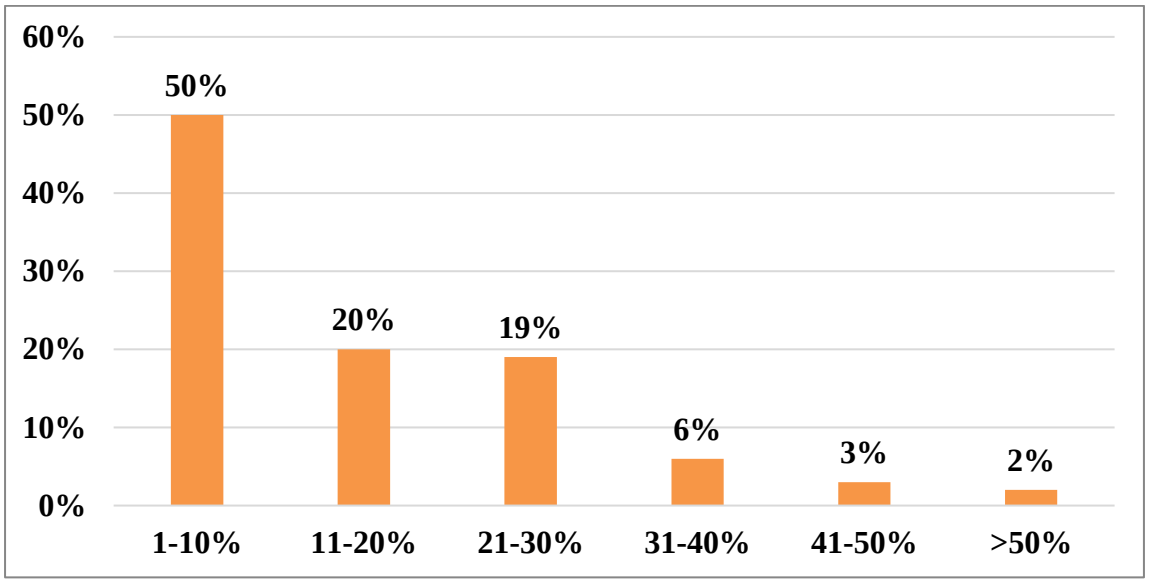
a. Yes
b. No
c. Sometimes



Majority of doctors, 65%, monitor serum P levels after administration of dydrogesterone in RPL.

9) In what % of your patients do you use dydrogesterone in RPL?

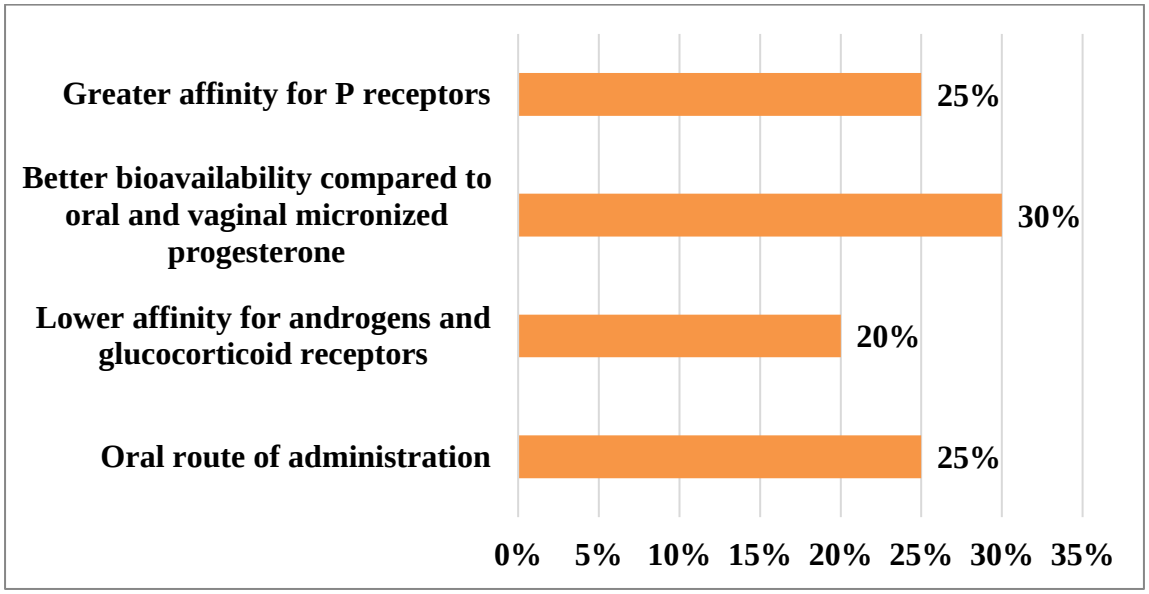
a. 1-10%
b. 11-20%
c. 21-30%
d. 31-40%
e. 41-50%
f. >50%



As per 50% of doctors, they use dydrogesterone in RPL in 1-10% of their patients.

10) According to you, which of the following are unique features ofdydrogesterone over conventional progestogens?

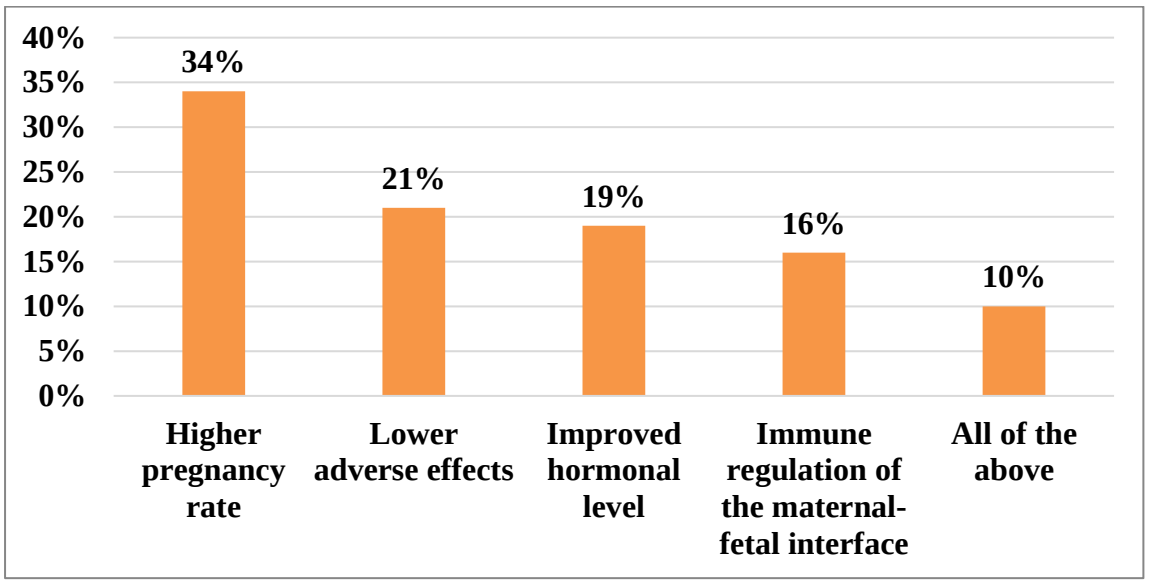
a. Oral route of administration
b. Lower affinity for androgens and glucocorticoid receptors
c. Better bioavailability compared to oral and vaginal micronized progesterone
d. Greater affinity for P receptors



According to 30% of doctors, the unique feature ofdydrogesterone over conventional progestogens is better bioavailability compared to oral and vaginal micronized progesterone.

11) What are the important benefits of using dydrogesterone in RPL?

a. Higher pregnancy rate
b. Lower adverse effects
c. Improved hormonal level
d. Immune regulation of the maternal-fetal interface
e. All of the above

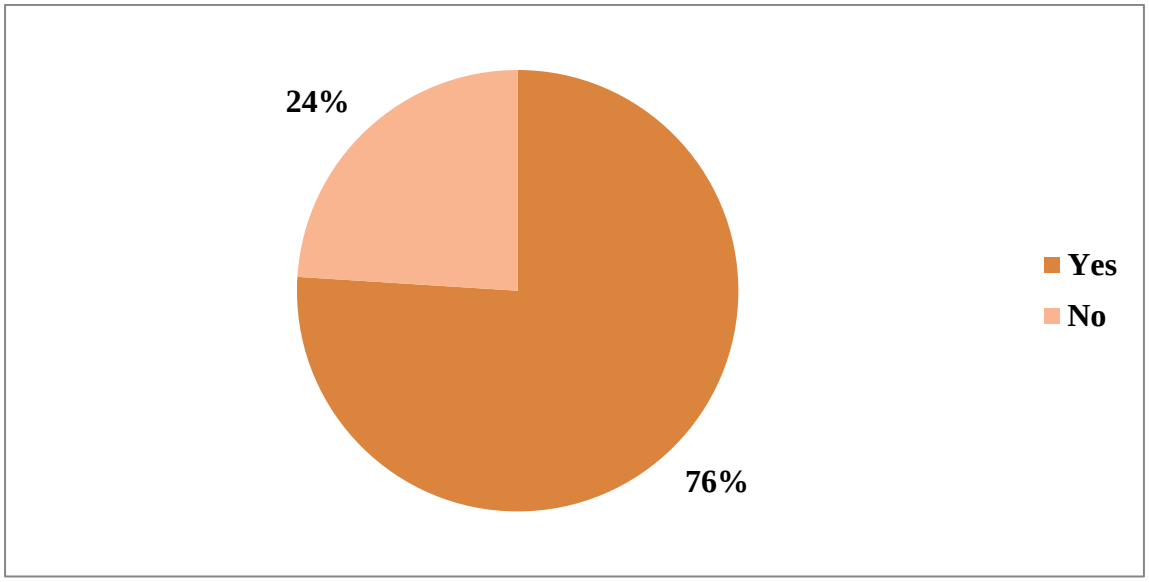


According to 34% of doctors, higher pregnancy rate is an important benefit of using dydrogesterone in RPL.

12) In the past, have you used Dydroeva in your practice?

a. Yes

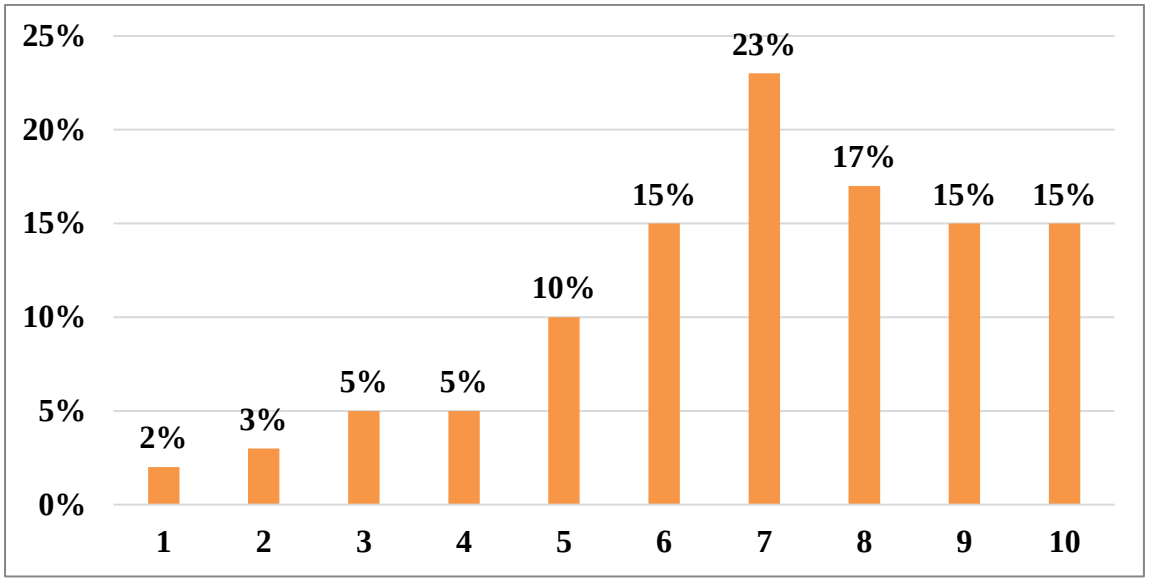
b. No



Majority of doctors (76%) have used Dydroeva in their practice.

13) How would you rate your experience (in terms of efficacy) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best)?

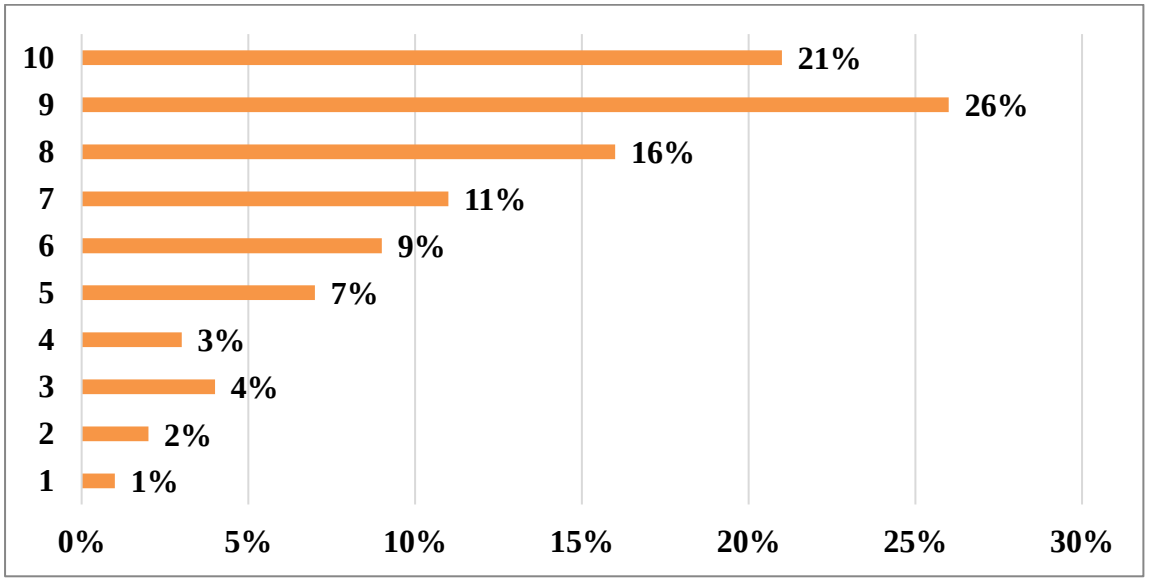
a. 1
b. 2
c. 3
d. 4
e. 5
f. 6
g. 7
h. 8
i. 9
j. 10



23% of doctors rate their experience (in terms of efficacy) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best) as 7.

14) How would you rate your experience (in terms of safety) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best)?

a. 1
b. 2
c. 3
d. 4
e. 5
f. 6
g. 7
h. 8
i. 9
j. 10



26% of doctors rate their experience (in terms of safety) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best) as 9.

Summary

- 25% of doctors encounter 5 – 10% cases of Recurrent Pregnancy Loss (RPL) in your practice.
- According to majority of doctors, 63%, primary pregnancy loss cases of RPL are commonly seen in their practice.
- As per 35% of doctors, the common risk factors for RPL is female age >40 years.
- According to 35% of doctors, most preferred type of progestogen in recurrent pregnancy loss is Dydrogesterone.
- Majority of doctors, 91%, use dydrogesterone in Recurrent Pregnancy Loss (RPL).
- Majority of doctors, 69%, use dydrogesteron in combination with oral/vaginal micronized progesterone in their patients with RPL.
- As per 30% of doctors, the preferred dose of dydrogesterone in RPL is 10 mg BID from the onset of bleeding until the 16th week of pregnancy.
- Majority of doctors, 65%, monitor serum P levels after administration of dydrogesterone in RPL.
- As per 50% of doctors, they use dydrogesterone in RPL in 1-10% of their patients.
- According to 30% of doctors, the unique feature ofdydrogesterone over conventional progestogens is better bioavailability compared to oral and vaginal micronized progesterone.
- According to 34% of doctors, higher pregnancy rate is an important benefit of using dydrogesterone in RPL.
- Majority of doctors (76%) have used Dydroeva in their practice.
- 23% of doctors rate their experience (in terms of efficacy) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best) as 7.
- 26% of doctors rate their experience (in terms of safety) with Dydroeva in RPL on a scale of 1-10 (1 being worst, 10 being best) as 9.

Consultant Opinion

Market Opportunities:

- There is a significant patient population affected by RPL, with 25% of doctors encountering 5 – 10% cases in their practice. This highlights the need for effective treatment options and interventions in this area.

Value for Healthcare Professionals:

- Healthcare professionals can benefit from continued education and training on the management of RPL, including the identification of risk factors, appropriate diagnostic procedures, and evidence-based treatment options.

Adverse Effect Management:

- Healthcare professionals should be vigilant in monitoring patients for potential adverse effects associated with RPL treatments, such as dydrogesterone. Providing guidance on adverse effect management and patient education can enhance treatment safety and adherence.

Withdrawal Management:

- In cases where discontinuation of treatment is necessary, healthcare professionals should implement appropriate withdrawal management strategies to minimize potential risks and adverse effects for patients.

Market Positioning:

- Pharmaceutical companies can position their products, such as Dydroeva, as effective and safe treatment options for RPL. Emphasizing the unique features and benefits of these medications can differentiate them in the market and increase their adoption by healthcare professionals.

Personalized Treatment Decisions:

- Healthcare professionals should adopt a personalized approach to treatment decisions for patients with RPL, considering individual patient characteristics, preferences, and treatment goals. This may involve tailoring treatment regimens, such as the dose and duration of dydrogesterone therapy, based on patient-specific factors.

Improving Patient Outcomes:

- Pharmaceutical companies and healthcare professionals should collaborate to develop and implement strategies aimed at improving patient outcomes in RPL. This may include conducting clinical trials to evaluate the efficacy and safety of novel treatment approaches, as well as providing comprehensive patient education and support resources.

In conclusion, there are significant opportunities for healthcare professionals and pharmaceutical companies to enhance patient care and outcomes in RPL through targeted interventions, personalized treatment approaches, and collaborative efforts to advance research and innovation in this field.

NOTES

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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