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Original Research Article

Dydrogesterone use in recurrent pregnancy loss and luteal phase insufficiency: a knowledge, attitude, and practice survey amongst Indian obstetricians and gynaecologists

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ABSTRACT

Background: Oral dydrogesterone is effective in treating reproductive disorders such as recurrent pregnancy loss (RPL) and is a better option than progesterone for luteal phase support (LPS) after in-vitro fertilization (IVF). This study aimed to assess the attitude, knowledge, and practice of obstetricians and gynecologists (ObGyns) across India towards the usage of dydrogesterone in RPL and LPS in real-life setting.
Methods: A validated questionnaire-based survey was conducted among Indian ObGyns and results were expressed in percentages.
Results: 393 ObGyns participated in the survey. 61.3% of ObGyns agreed RPL is the three consecutive pregnancy losses prior to 20 weeks from the last menstrual period. With the use of dydrogesterone in RPL patients, 82.6% of ObGyns found >40% of patients having successful pregnancy outcomes. 37.2% of ObGyns mentioned that dydrogesterone is useful in ongoing pregnancy rates while 33% reported benefits in the live birth rate. At the risk for preterm delivery before 34 gestational weeks, 57% of ObGyns see benefits of dydrogesterone. More than 95% of ObGyns observed benefits of dydrogesterone over micronized progesterone such as good efficacy, fewer side effects, better tolerability, and improved patient compliance. 51.9% of ObGyns reported that they used dydrogesterone in combination with progesterone in LPS.
Conclusions: The present KAP survey highlights the observation, perception, and practicing behaviour of ObGyns on RPL and LPS. It also highlights the usage of dydrogesterone in aforesaid indications.

Keywords: Dydrogesterone, KAP survey, Luteal phase support, Recurrent pregnancy loss

INTRODUCTION

Progesterone is involved in regulating the immune response of the mother for the prevention of embryo rejection and acts on the endometrium and uterus for the successful implantation of the embryo.[1] It is an essential hormone required for the initiation and maintenance of pregnancy.[2]

Dydrogesterone is an orally active progestogen similar to endogenous progesterone having a high affinity towards progesterone receptors. Receptor selectivity and superior bioavailability of dydrogesterone minimize the clinical dose and are reported to be 10-20 times lower oral dose than progesterone.[1]

Oral dydrogesterone emerges as a safe and effective treatment choice for patients with Recurrent spontaneous abortion.[1] Clinical studies showed oral dydrogesterone has comparable efficacy as micronized vaginal progesterone for luteal phase support (LPS) and hence serves as an alternative to micronized vaginal progesterone for LPS.[3]

Recurrent pregnancy loss (RPL), also known as recurrent miscarriage or habitual abortion, occurs in 2.5% of women who are trying to conceive.[4] Genetic factors, autoimmune disorders, endocrine disorders, and structural uterine abnormalities are some of the risk factors responsible for RPL. No risk factors are identified in >50% of women. Despite various mechanisms involved in the RPL pathophysiology all of which may ultimately lead to a common pathway that causes pregnancy loss.[4]

In Luteal-phase deficiency, inadequate endogenous progesterone during embryo implantation leads to infertility and pregnancy loss. It has been revealed that ovarian hyperstimulation cycles lead to a defective luteal phase. For In-Vitro Fertilisation (IVF) several treatment protocols have been adopted to improve pregnancy outcome. However, the ideal treatment, the right dose, and the best time for initiating LPS in the IVF cycle are controversial.[5]

Given the limited available data on dydrogesterone's utilization in RPL and LPS among Indian clinicians, this survey aims to explore the knowledge, perceptions, and usage of dydrogesterone by Indian obstetricians and gynaecologists (ObGyns) in real-world setting. The objective of this survey was to understand the knowledge of Indian ObGyns about the RPL. The attitude assessment section refers to the outlook of the ObGyns towards the efficacy and tolerability of dydrogesterone. The practice section describes the usage pattern of dydrogesterone in regular clinical practice.

METHODS

This was a prospective, cross-sectional, observational, questionnaire-based survey conducted among Indian ObGyns. A survey questionnaire consisted of 11 multiple-choice questions on various practical aspects of RPL, luteal phase defects (LPD), and usage of dydrogesterone in RPL and LPD. A meeting was conducted on the virtual platform for 15 seniors ObGyns with at least 25 years of clinical experience. The survey questionnaire was discussed and developed by these experts. Further, these questions were validated by all the members of this group.

The survey was carried out from February 2020 to December 2021. Participants of the survey were registered medical practitioners who have recognized qualifications in obstetrics and gynecology (DGO/MD/MS) working in the outpatient departments of private clinics/hospitals in a tertiary care settings comprising all over India. The questionnaire was circulated in person to ObGyns at their respective clinics/hospitals situated in various states of India. The survey questionnaire was filled in by ObGyns, based on their prior clinical experience and knowledge of the usage of dydrogesterone in RPL and LPS.

Data were collected, analyzed, summarised in percentages, and presented as tables and/ or graphs. As this was a survey and no patient-related data was captured therefore ethics committee approval was not necessary and hence not obtained.

RESULTS

A total of 393 ObGyns participated in this survey across India and all of them completed the survey. The ObGyns participated in the survey were located from 22 different states of India. Overall, 25.4% ObGyn participants were from East, 41.5% from West, 12.4% from North, and 20.7% from South zone. A total of 299 centers across India were involved in this survey. The responses from the participants were evaluated and analyzed as follows:

Knowledge assessment

Recurrent pregnancy loss (RPL)

Criteria for defining RPL

The definition of RPL has long been debated and differs among international societies. About 61.3% of ObGyns agreed to the definition of RPL as three consecutive pregnancy losses prior to 20 weeks from the last menstrual period whereas, 38.7% agreed on RPL as, two or more clinical pregnancy losses (documented by ultrasonography or histopathologic examination), but not necessarily consecutive.

Risk factors associated with RPL

Several risk factors are responsible for RPL like advanced maternal and paternal age, obesity, genetic abnormalities, lifestyle factors, diabetes, endometriosis, PCOS, and hereditary thrombophilia. According to this survey responses genetic abnormalities contribute to 20.9%,

followed by advanced maternal age (13.7%), and lifestyle factors (10.8%) for RPL (Table 1).

Table 1: Risk factors associated with recurrent pregnancy loss.

Risk factors associated with recurrent pregnancy loss	% of Association
Advanced maternal age	13.7
Advanced paternal age	7.7
Obesity	9.6
Genetic abnormalities	20.9
Lifestyle factors	10.8
Diabetes	9.8
Endometriosis	8.8
PCOS	10.0
Hereditary thrombophilia	8.8

Incidence of RPL according to women's age

Subsequently, almost 25% of the ObGyns reported that >40 years age group has more incidences of RPL whereas 42.7 % of the ObGyns reported that the incidence of RPL is between 31-40 years of the age group enumerated in Figure 1.

Attitude assessment

Benefits of dydrogesterone

The success rate of dydrogesterone usage in RPL

Dydrogesterone is used in patients with RPL in clinical practice. In our survey, 82.6% of ObGyns reported that after usage of dydrogesterone successful pregnancy outcome was in more than 40% of patients. Whereas, 17.3% of ObGys reported successful pregnancy outcomes after usage of dydrogesterone was in below 40% of patients (Figure 2).

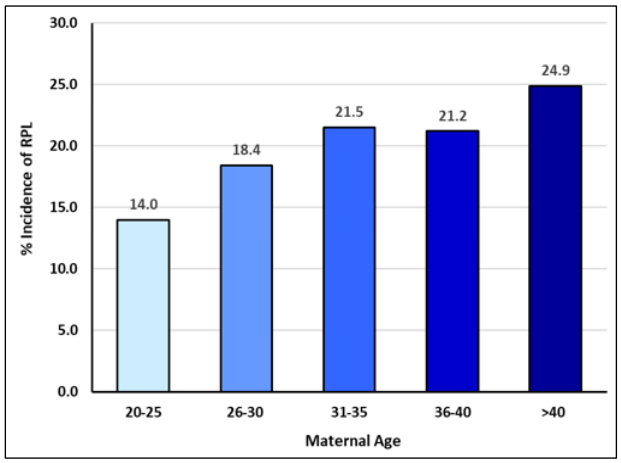

Figure 1: Percentage incidence of recurrent pregnancy loss according to maternal age group.

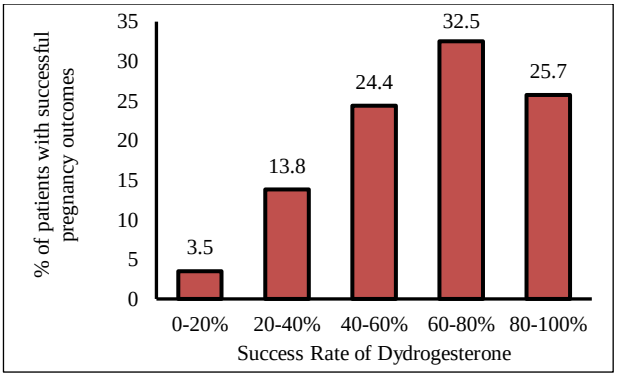

Figure 2: The success rate of dydrogesterone use in recurrent pregnancy loss patients.

Benefits of dydrogesterone treatment in IVF cases

Continuation of dydrogesterone usage in IVF has few pregnancy outcome benefits. The majority of responses i.e. 37.2% ObGyns reported dydrogesterone has a benefit in ongoing pregnancy rate followed by 33% reported that dydrogesterone has a benefit in live birth rate, while 30% ObGyns stated its benefit in implantation rate.

Benefits of dydrogesterone in gynecological conditions

About 57% of responses from ObGyns reported that they observed benefits of dydrogesterone in the risk of preterm birth before 34 gestation weeks whereas 25.7% of responses from ObGyns reported that they observed benefits in the incidence of low birth weight. While 17.4% of ObGyns observe benefits in perinatal mortality.

Benefits of dydrogesterone over micronized progesterone

Dydrogesterone has benefits like good efficacy, fewer side effects, better tolerability, and improved patient compliance. More than 95% of ObGyns reported that they observed all the benefits of dydrogesterone over micronized progesterone i.e. increased efficacy, better tolerability, fewer side effects, and improved patient compliance (Figure 3).

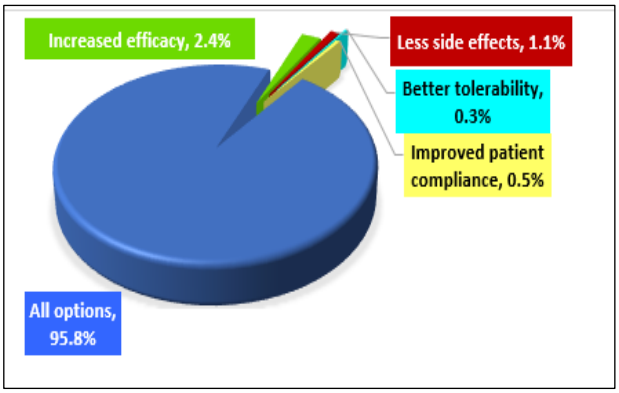

Figure 3: Percentage response for the benefits of dydrogesterone over micronized progesterone.

Tolerability of dydrogesterone

Adverse drug reactions (ADRs) of oral micronized progesterone over dydrogesterone

When a survey for ADRs for oral micronized progesterone over dydrogesterone was carried out, it was reported that headache (27.1%) was the most common ADR observed higher incidence for oral micronized progesterone over dydrogesterone. Followed by headache, upset stomach (19.6%), breast tenderness or pain (18.2%), and tiredness (15.5%) were the few most frequent ADRs reported by the study participants with oral micronized progesterone usage (Table 2).

Table 2: Adverse drug reactions associated with micronized progesterone usage over dydrogesterone.

Adverse drug reactions	% of response
Headache	27.1
Breast tenderness or pain	18.2
Upset stomach	19.6
Vomiting	18.7
Diarrhea	3.9
Constipation	12.3
Tiredness	15.5
Muscle, joint, or bone pain	7.2

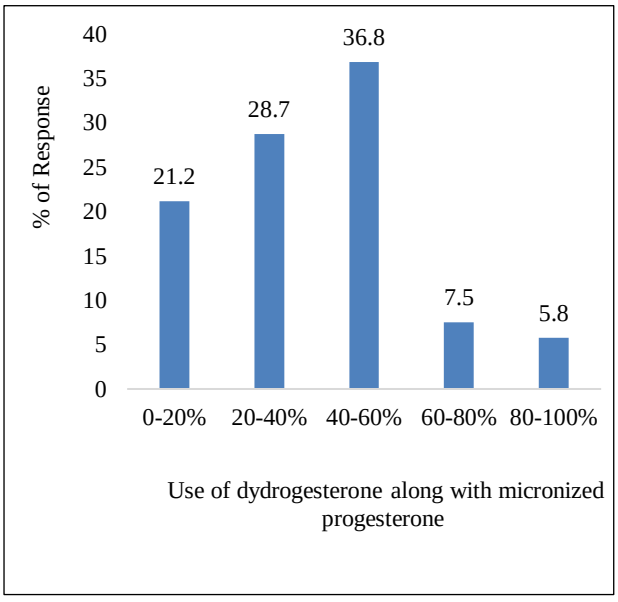

Figure 4: Percentage response for preference of usage of dydrogesterone along with the micronized progesterone.

Limitations for vaginal progesterone

In this survey, 64.4% ObGyns reported that poor patient compliance is the most common limitation associated with the use of vaginal progesterone whereas 60.8% ObGyns reported that inconvenience to the users, 49.4% reported ADRs like vaginal itching and discharge, and 32.8% ObGyns reported it is not acceptable by the patients. These limitations restrict the use of vaginal progesterone.

Practice assessment

Luteal phase support (LPS) in assisted reproductive technology

The preferred treatment for LPS in IVF cases

About 82.7% of ObGyns preferred the use of dydrogesterone in IVF for LPS. Of them, 51.9% of the ObGyns preferred dydrogesterone along with progesterone whereas 30.8% of them mentioned it is used alone in their practice in IVF for LPS. Further 8.1% of ObGyns reported the use of progesterone along with estrogen, 6.1% reported the use of progesterone alone, and 3.1% reported the use of progesterone along with GnRH (gonadotropin releasing hormone) agonists in the treatment of LPS in IVF cases.

General practice

Use of dydrogesterone along with micronized progesterone

Generally, dydrogesterone is used along with progesterone in clinical practice. In this survey, 49.9% of ObGyns reported they used a combination of dydrogesterone and micronized progesterone in less than 40% of patients while 50.1% of ObGys preferred the combination in more than 40% of patients (Figure 4).

DISCUSSION

Several studies found that dydrogesterone treatment had a positive effect on RPL, LPS, increased pregnancy rates, and improved reproductive outcomes.[6,7] With the limited data on its usage in India, it is relevant to evaluate the current knowledge, attitude, and practice of Indian ObGyns about the use of dydrogesterone. Hence present KAP survey was carried out to evaluate the approach of ObGyns toward the role of dydrogesterone in the treatment of RPL and LPS. The present survey highlighted the efficacy of dydrogesterone in the treatment of RPL and also its use in LPS in IVF treatment. The benefits of dydrogesterone, its use in combination with micronized progesterone, the tolerability of oral micronized progesterone, and the limitations of vaginal progesterone were also discussed.

In the present survey, the most preferred criteria to define the RPL by Indian ObGyns was studied. It was observed that three consecutive pregnancy losses prior to 20 weeks from the last menstrual period were the most preferred criteria to define RPL among Indian ObGyns. This criterion of three or more consecutive miscarriages is in alignment with the World Health Organisation (WHO) and the Royal College of Obstetricians and Gynecologists (RCOG).[8] Whereas, in contrast to this, ASRM (American

Society for Reproductive Medicine) and ESHRE (European Society for Human Reproduction and Embryology), defined RPL as two or more clinical pregnancy losses (documented by ultrasonography or histopathologic examination), but not necessarily consecutive.[8] This definition was preferred by 38.7% ObGyns of the present survey. In India, it is important to use a uniform criterion to define the RPL to exactly identify the incidence rate of RPL in the Indian population, so a consensus is needed amongst Indian ObGyns in this regard.

It is estimated that genetic disorders contribute 25% of risk factors in RPL.[9] The ObGyns of the present survey also emphasized that genetic abnormalities are the major risk factors responsible for RPL followed by advanced maternal age. The risk of RPL increases almost linearly >30 years of women's age reaching to a risk of 54% at the age ≥45 years.[10] Similarly, the majority of the ObGyns in this survey agreed to the fact that >30 years age group of women has more incidences of RPL whereas <30 years age group has fewer incidences of RPL. Further almost 25% of the ObGyns reported that >40 years age group has more incidences of RPL.

In the present survey, the majority of the ObGyns (82.6%) reported that successful pregnancy outcomes were observed in more than 40% of RPL patients who had received dydrogesterone. Kale and colleagues also observed a higher number of patients getting oral dydrogesterone had a successful continuation of pregnancy up to 24 weeks of gestation, as well as till full term compared to the progesterone group.[11]

It has been evident that progestin seems to be a better option for preventing the initiation of preterm labor and treating it once it is already established. In the present survey, 57% of ObGyns stated that dydrogesterone treatment has benefits in reducing the risk of preterm birth (<34 weeks). Studies on dydrogesterone treatment in women with a risk of preterm delivery showed increased production of progesterone-induced blocking factor and Th2 cytokines, and lower concentrations of Th1 cytokines, which could be effective for the prevention or treatment of pre-term labor.[12]

Dydrogesterone treatment has several benefits compared to other progestogens in terms of pharmacokinetic parameters, administration route, efficacy, and safety profile.[3] More than 95% of ObGyns reported that they observed the benefits of dydrogesterone like increased efficacy, fewer side effects, better tolerability, and improved patient compliance compared to micronized progesterone in clinical practice.

Dydrogesterone is a substitute for progesterone for LPS in IVF-ART. When the benefits of dydrogesterone were evaluated in the IVF patients, 37.2% of ObGyns reported that dydrogesterone usage has benefits in ongoing pregnancy followed by 33% reported it has benefits in the live birth rate. The benefit is in alignment with a study that showed a higher pregnancy rate and live birth rate in oral dydrogesterone group compared to micronized vaginal progesterone group for LPS in IVF.[3] MIDRONE trial suggested that the addition of oral dydrogesterone to vaginal progesterone as LPS in IVF with frozen embryo transfer cycles reduced the miscarriage rate and improved the live birth rate.[13] In this survey, 51.9% of ObGyns preferred dydrogesterone along with progesterone, and 30.8% of ObGyns selected dydrogesterone monotherapy as the treatment option for the LPS in IVF patients.

In most clinical settings, dydrogesterone is prescribed in combination with progesterone to improve pregnancy outcomes. Whereas, most of the ObGyns reported in this survey that they are marginally using dydrogesterone along with micronized progesterone in their general clinical practice. ObGyns of the present survey also reported that oral micronized progesterone has a higher incidence of ADRs such as headache, upset stomach, breast tenderness or pain, and tiredness compared to dydrogesterone.

Most of the ObGyns of this survey confirmed poor patient compliance and inconvenience to the users are the biggest limitations with the use of vaginal progesterone. These limitations of vaginal progesterone restrict its use in clinical practice. Overall inconvenience, administration-related side effects, and cultural barriers are some of the issues associated with the vaginal progesterone.[3] Convenience and tolerability are the two important criteria for the use of any drug which affects the patient's adherence to the treatment and ultimately its effectiveness.

Senior ObGyns were involved in designing and validating the questionnaire. The survey participants i.e. a large number of ObGyns from different states of India were involved the present study, which was the main feature of this survey. The survey questions were based on the real-life experience of ObGyns. Pre-decided questions with pre-decided options is the main limitation of the study. Also recall bias is one of the limitation. This survey emphasized that many ObGyns were shown their experience in defining the RPL and the risk factors associated with it. According to this survey, the majority of the ObGyns based on their clinical experience reported that the use of dydrogesterone in ongoing pregnancy contributes to successful pregnancy outcomes in women with a history of RPL. The majority of the ObGyns reported usage of dydrogesterone has successful pregnancy outcomes in RPL and LPS. Similarly, most of the ObGyns shared their clinical experience of the usage of dydrogesterone in LPS. They preferred dydrogesterone alone and in combination with micronized progesterone in LPS patients undergoing IVF. Also, reported the benefits of dydrogesterone over micronized progesterone. This real-life experience survey on the usage of dydrogesterone will be helpful for ObGyns in the clinical management of RPL and LPS.

CONCLUSION

A knowledge question from this survey highlighted that a consensus on the clinical definition of RPL is necessary to maintain uniformity throughout the country. The present KAP survey emphasized the role of dydrogesterone in RPL and LPS. Many of the Indian ObGyns highly rated dydrogesterone usage in RPL and LPS with successful pregnancy outcomes. The majority of ObGyns of the present study agreed that increased efficacy, fewer side effects, better tolerability, and improved patient compliance are some of the benefits of dydrogesterone over micronized progesterone. Indian ObGyns preferred dydrogesterone either alone or in combination with progesterone for LPS in IVF cases. Further ObGyns reported marginal use of dydrogesterone along with micronized progesterone in their general clinical practice. Subsequently, this real-life KAP survey of ObGyns across India highlights effectiveness, tolerability, and usage patterns that will be helpful for the ObGyns about the utility of dydrogesterone in the clinical management of RPL and LPS.

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