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Original Research Article

Dydrogesterone usage pattern in India: a knowledge, attitude and practice survey among Indian gynaecologists

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ABSTRACT

Background: There is limited data about the knowledge, perception, and routine clinical usage pattern of dydrogesterone among medical practitioners in India. Therefore, the present survey was undertaken to assess attitudes and perception/practices of obstetrician and gynaecologists towards use of dydrogesterone in the real-life setting.

Methods: Total 1168 gynaecologists across India participated in the KAP survey. Sixteen questions which explored indications, dosages, duration, efficacy, tolerability and comparison were asked and results were expressed as percentages.

Results: Dydrogesterone has been marketed since the 1960s and has been extensively used worldwide for the treatment of threatened miscarriage (TM) and recurrent miscarriage (RM). Dydrogesterone is approved for hormone replacement therapy (HRT), as well as pregnancy and non-pregnancy-related conditions where there is a progesterone deficiency. In the present survey, dydrogesterone 10 mg twice daily was found to be the most commonly preferred dosage by 823 (73%) gynaecologists. Poor tolerability, compliance and lower efficacy were reported as major limitations of micronized progesterone by 68% of doctors. The average clinical pregnancy rate noted at 12 weeks after Dydrogesterone usage was around 40% by majority of the doctors. However, 30% of doctors noted more than 40% of clinical pregnancy rate after dydrogesterone usage. Almost 35% of doctors reported that the average live birth rate noticed after dydrogesterone usage is around 40%.

Conclusions: The present KAP survey highlights that the effectiveness and the tolerability of dydrogesterone is valued by Indian gynaecologists which accounts for its robust clinical utility.

Keywords: KAP survey, Threatened miscarriage, Recurrent miscarriage, Luteal phase support, India

INTRODUCTION

Progesterone is required for creating a suitable endometrial environment for embryo implantation and for the maintenance of pregnancy. Progesterone is also

believed to help in mediating an anti-inflammatory immune response to the allogenic foetus and in inducing uterine smooth muscle relaxation.¹⁻³ Progestogens have been used extensively in an attempt to overcome progesterone deficiency associated with infertility and

miscarriage.³ Different progestogens varies in their progestogenic potency, receptor-binding selectivity, bioavailability, and route of administration and these factors determine selection of the most appropriate agent for each condition.³ Micronized progesterone is in use since 1980s.⁴ Because of low and variable bioavailability, micronized progesterone is administered orally with high doses, which results in side effects such as drowsiness, nausea, and headaches.⁵ With these reasons, micronized progesterone is typically administered vaginally. However intravaginal micronized progesterone may not be fully absorbed, may be washed out with vaginal bleeding, and may cause local irritation.⁶

So, alternative progestogens have become widely used for obstetric indications. One of those is dydrogesterone or 6-dehydro-retroprogesterone, which has a molecular structure closely related to that of natural progesterone.³ It is administered orally and has reported 5.6 times higher bioavailability than that of progesterone.⁷ Dydrogesterone is highly selective for the progesterone receptor.³ It is estimated that dydrogesterone requires a 10–20 times lower oral dose compared with micronized progesterone.³ Currently there is limited data about the knowledge, perception, and routine clinical usage pattern of dydrogesterone among medical practitioners in India. The present survey was undertaken to explore the knowledge, perception, and usage of dydrogesterone by Indian gynaecologists in the real-life setting. The aim of this survey was to study the usage of progesterone in current clinical practice, and to study the advantages of dydrogesterone over natural micronized progesterone.

METHODS

Survey design and setting

This was a prospective, cross-sectional, observational, questionnaire-based survey conducted across India from December 2020 to Feb 2021. The flow of the study was: administration of the questionnaire to Obstetrician and Gynaecologist who gave consent, followed by filling of questionnaire based on prior clinical experience and knowledge of usage of dydrogesterone, collection of questionnaires, compilation, analysis and presentation of data.

Survey participants

The KAP survey was facilitated by the authors. Registered medical practitioners with recognized qualifications in Gynaecology and working in outpatient departments of public and privately run clinics/hospitals participated in this survey. The survey consisted of total 1168 gynaecologists across all over India.

Survey instrument

The survey questionnaire was specially designed, self-completion and structured, which included 16 multiple

choice questions. The survey assessed the gynaecologists' knowledge, attitude, and practice toward the use of dydrogesterone in routine clinical practice. It was a voluntary survey and therefore it was not necessary to answer all the questions and participants were free to choose more than one response to a question if desired and suitable.

Knowledge here refers to knowledge about dydrogesterone. The knowledge based questions were as followed: Average number of patient with recurrent pregnancy loss in a month, patients most suitable for treatment with dydrogesterone, % of patients requiring treatment with dydrogesterone, preferred dose of dydrogesterone and most important and critical factors for selecting dydrogesterone in routine clinical practice.

Attitude refers to the outlook of obstetrician and gynaecologist towards the efficacy and tolerability of dydrogesterone. The attitude based questions were as followed: limitations towards use of micronized progesterone in clinical practice, advantages of dydrogesterone over natural micronized progesterone, average clinical pregnancy rate noticed at 12 weeks after dydrogesterone usage and average live birth rate noticed after dydrogesterone usage.

The remaining seven questions related to practice were:

Preferred type of progesterone in clinical practice, average duration of dydrogesterone therapy used in case of recurrent miscarriage, duration for use of dydrogesterone in threatened abortion, preferred area for use of natural micronized progesterone, preference and conditions for co-administration of dydrogesterone and natural micronized progesterone and preference on indigenously developed products. This was a survey through which no patient related data was captured and therefore ethics committee approval was not necessary and hence not obtained. As this was not a clinical trial, no clinical trial registration was required.

Data analysis

Descriptive statistics were used to summarize the qualitative data by number (n) and percentage for each category in each question. This data was graphically represented as bar diagrams. Not all participants answered all the questions and many participants responded to more than one option for many of the questions if desired and suitable. The denominator for calculating proportion for a particular question was total number of participants replied to a particular question and the 'n' has been appropriately marked in each graph.

RESULTS

Total 1168 Obstetrician and gynaecologists participated in this survey across India, out of whom, all 1168 completed the survey.

Table 1: Average dose of dydrogesterone.

Average dose of dydrogesterone	No. of doctors	%
10 mg once daily	171	15
10 mg two times daily	823	73
10 mg three times daily	117	10
20 mg twice daily	33	3
Other	6	1

Table 2: Preference on indigenously developed product.

Preference on indigenously developed product	No. of doctors	%
Most preferred	421	38
Preferred	476	43
Neutral	110	10
Does not matter	108	10
Total preference on indigenously developed product (most preferred + preferred)	897	81

Table 3: Factors for selection of Dydrogesterone.

Factors for selection of dydrogesterone	No. of doctors	%
Quality of product	514	46
Clinical data	229	20
Patient related outcomes	478	43
Cost	211	19
Other	31	3

Data from 688 (59%) centres reports that, approximately 20 women with recurrent pregnancy loss usually visited every month. Dydrogesterone 10 mg twice daily was the most commonly preferred dosage by 823 (73%) of gynaecologists, while 171 (15%) and 117 (10%) of gynaecologists preferred to use 10 mg OD and 10 mg TID dosage of dydrogesterone respectively (Table 1).

Interestingly, 87% gynaecologists reported to use dydrogesterone in women with recurrent pregnancy loss, habitual abortion, threatened abortion and for luteal phase support (Figure 1). Near about 474 (42%) of the gynaecologists reported to use dydrogesterone for up to 14 weeks in women with threatened abortion while 371 (33%) of gynaecologists preferred to use dydrogesterone till 18 weeks in women with threatened abortion (Figure 2). Near about 412 (36%) of the gynaecologists reported to use dydrogesterone in recurrent miscarriage for up to 10 to 14 weeks (Figure 3).

Total 337 (30%) gynaecologists reported more than 40% of clinical pregnancy rate after 12 weeks of dydrogesterone usage (Figure 4). While, total 388 (35%) gynaecologists reported the average live birth rate observed after 12 weeks dydrogesterone usage was 40% (Figure 5).

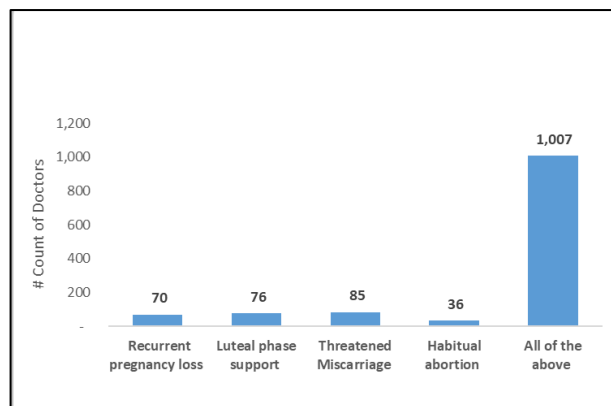


Figure 1: Most suitable conditions for use of dydrogesterone.

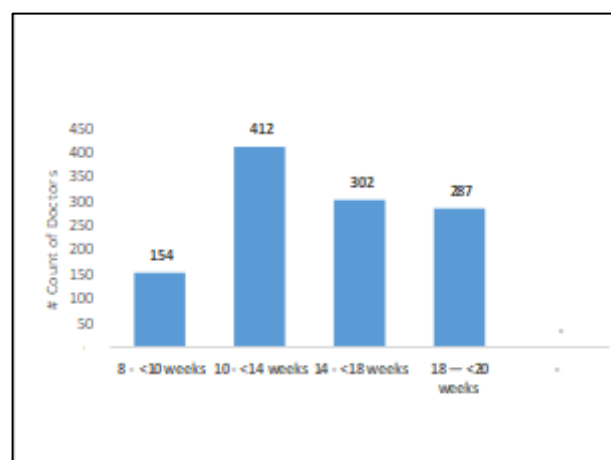


Figure 2: Average duration of dydrogesterone therapy in threatened abortion.

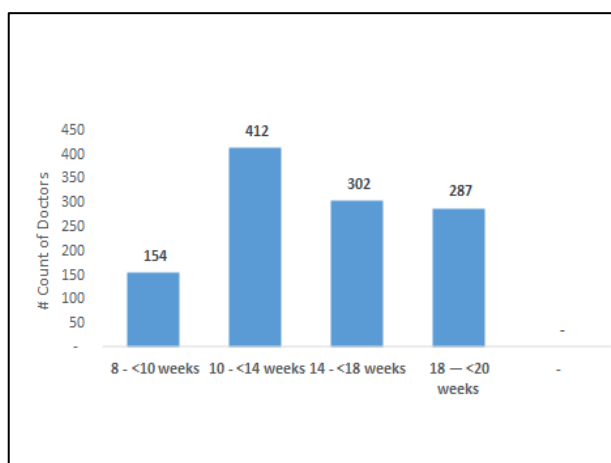


Figure 3: Average duration of dydrogesterone used in of recurrent miscarriage.

Majority of doctors i.e. 817 (72%) reported high bioavailability, higher compliance, low side effects and better quality of life as advantages of dydrogesterone over micronized progesterone (Figure 6). Out of all participants, the indigenously developed product was the

most preferred or preferred choice of around 897 (81%) of gynaecologists (table 2). Poor tolerability, compliance and lower efficacy were the major limitations for use of micronized progesterone reported by 743 (68%) gynaecologists.

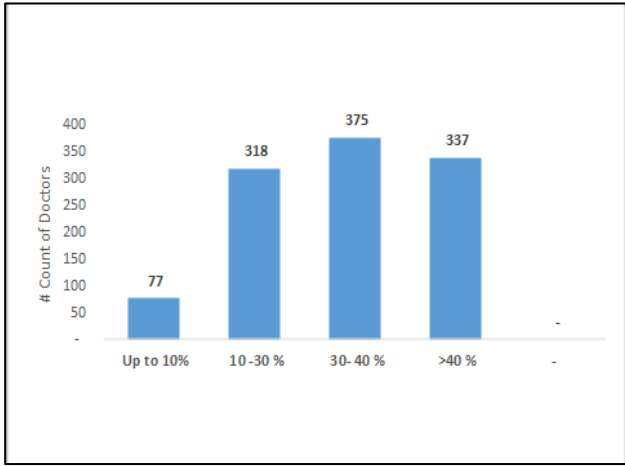


Figure 4: Average clinical pregnancy rate noticed at 12 weeks of dydrogesterone.

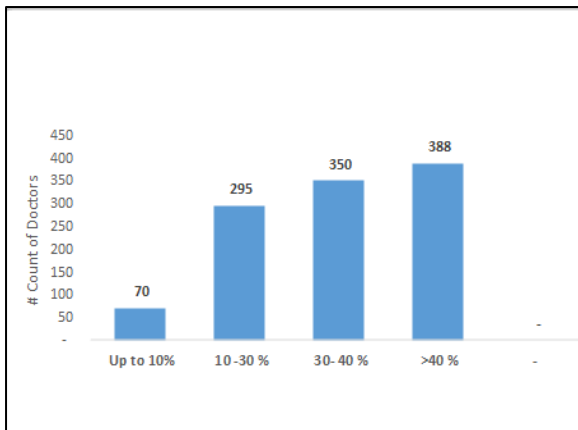


Figure 5: Average live birth rate observed after 12 weeks of dydrogesterone usage.

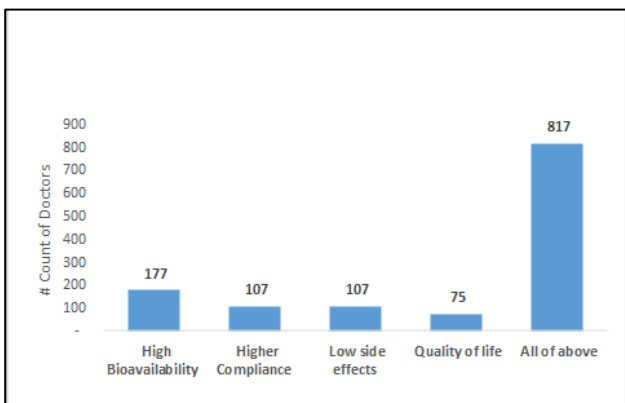


Figure 6: Advantages of dydrogesterone over natural micronized progesterone.

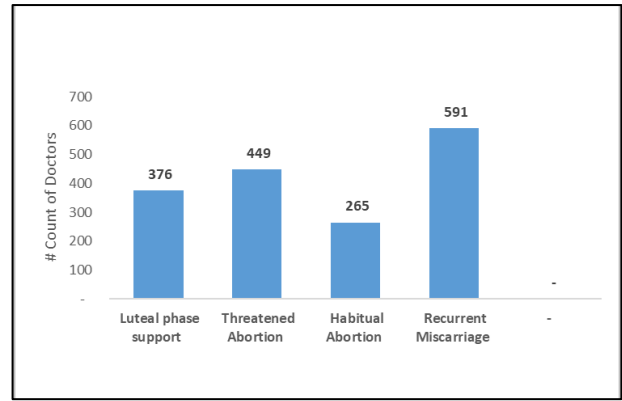


Figure 7: Co-administration of dydrogesterone and natural micronized progesterone in different indications.

Almost 771 (70%) of doctors preferred to use dydrogesterone along with micronized progesterone. Dydrogesterone and micronized progesterone were preferred to be co-administered in recurrent miscarriage, threatened abortion and luteal phase support by 54%, 41% and 35% of doctors respectively (Figure 7). In this survey the quality of product and patient related outcomes were found to be two most important factors for selecting dydrogesterone by 514 (46%) and 478 (43%) gynaecologists respectively (Table 3). Whereas cost was not considered as an important Table 3.

DISCUSSION

Dydrogesterone has been marketed since the 1960s and has been extensively used worldwide for the treatment of threatened miscarriage and recurrent miscarriage, as well as for luteal phase support in the setting of infertility.⁷ Similar findings were observed in this survey wherein the substantial proportion of Indian gynecologists i.e. 87% reported to use dydrogesterone in women with recurrent pregnancy loss, habitual abortion, threatened abortion and for luteal phase support.

Many reports suggest that oral administration is most convenient for patients over intravaginal application and similar trends were observed in this survey.⁷⁻¹⁰ The oral progesterone and its derivative was preferred by around 42% of the doctors while only 7% and 3% of doctors preferred to use vaginal and injectable progesterone respectively.

Clinical studies have shown that oral dydrogesterone has a good benefit-risk profile, comparable to that of micronized vaginal progesterone.¹¹ In this survey high bioavailability, high compliance, low side effects and better quality of life were reported as advantages of dydrogesterone over micronized progesterone by 72% of doctors. While poor tolerability, compliance and lower efficacy were reported as major limitations of micronized progesterone by 68% of doctors. In terms of efficacy of dydrogesterone in comparison to MVP, the results of 2013

Cochrane Systematic Review suggests that dydrogesterone may be more effective than vaginal micronized progesterone in preventing miscarriage (8.0% and 15.7% of women miscarried, respectively).¹² While in the landmark trials like Lotus I and Lotus II it was demonstrated that oral dydrogesterone was non-inferior to micronized vaginal progesterone.^{13,14} Both the Lotus I and Lotus II studies have also demonstrated that oral dydrogesterone and MVP had comparable safety and tolerability profiles. In this survey, majority of the Indian gynaecologists reported that the average clinical pregnancy rate noted at 12 weeks after dydrogesterone usage is around 40% and around 30% of doctors noted more than 40% of clinical pregnancy rate after dydrogesterone usage.

The live birth rate noticed after dydrogesterone usage was also around 40% by almost 35% of doctors. Interestingly, almost 70% of Indian gynaecologist reported to use dydrogesterone along with micronized progesterone. The most common indications reported for co-administration of dydrogesterone and micronized progesterone were recurrent miscarriage, threatened abortion and luteal phase support reported by 54%, 41% and 35% of doctors respectively.

In the current survey, on points of clinical utility of dydrogesterone, 10 mg twice daily was the most commonly preferred dosage by 823 (73%) of gynecologists. In women with recurrent miscarriage, 52% of doctors preferred to continue treatment with dydrogesterone for up to 18 to 20 weeks. While in cases of threatened abortion, near about 42% of the doctors reported to use dydrogesterone up to 14 weeks and 33% of doctors preferred to use dydrogesterone till 18 weeks in women with threatened abortion.

Another interesting finding of this survey was that the quality of product and patient related outcomes were found to be two most important factors for selecting dydrogesterone by 514 (46%) and 478 (43%) gynaecologists respectively, whereas cost was not considered as an important factor for selecting dydrogesterone.

Pan-India coverage and participation of a large number of gynaecologists are some of the strengths of this study. The present KAP study was cost-effective and the results were based on real life experiences. This study/survey has limitations which are applicable to a KAP study. A questionnaire reveals what is ticked but not necessarily what is actually practiced. Also, fixed number of questions with predefined options and recall bias were another limitations of the study. Present questionnaire was designed by authors and was not validated. This was designed to match observations in clinical practice. Questionnaire was based on a subjective opinion. Nevertheless, this was an attempt to understand the knowledge, attitude and practice of Indian gynaecologists towards use of dydrogesterone in clinical practice which

revealed some known and some new interesting facts. However, these findings must be considered cautiously and confirmed by clinical studies.

CONCLUSION

The present KAP survey highlights that effectiveness and tolerability of Dydrogesterone is valued by many Indian gynaecologists which accounts for its robust clinical utility.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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