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Original Research Article

Practice profile of Indian gynaecologists on the use of micronized progesterone and dydrogesterone in pregnancy and assisted reproductive technology cycles: progress survey

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ABSTRACT

Background: Though progesterone supplements are prescribed for Progesterone deficiency in pregnant and infertile women, there is ambiguity on the different forms of progesterone supplements prescribed in various conditions, duration, dosing regimen, etc. The aim of this survey was to gain insights into the practice profile of Indian Gynaecologists on progesterone supplements and the various factors governing these choices.
Methods: A total of 513 practicing gynecologists completed a digital survey on usage patterns of Micronized Progesterone (NMP) and Dydrogesterone (DYD) in pregnancy and Assisted Reproductive Technology (ART) cycles. Data were analyzed using suitable statistical tests.
Results: A total 48% and 41.9% prescribed DYD and NMP-sustained release (NMP-SR) in 20-50% patients respectively, and 58.5% prescribed NMP capsule in <20% patients. >50% gynaecologists prefer DYD as progesterone supplements for threatened abortion (TA), preterm birth (PTB), Recurrent abortion (RA), and luteal phase support (LPS) in ART. Patient's obstetrics history (26.2%), indication (18.6%), and route of administration / efficacy (12.2% each) were the top factors considered for prescribing progesterone supplements. 67.8% gynaecologists prescribe multiple progesterone preparations and of these 38.7% combined DYD + NMP-SR. 35.8% gynaecologists prefer DYD 10 mg thrice daily to prevent preterm labour in case of twin pregnancy, and 43.5% gynaecologists reported prescribing DYD 40 mg immediately followed by 30mg/day for 7 days in TA.
Conclusions: This survey provided insights into usage patterns of oral and vaginal Progesterone preparations in PTB, TA, RA and LPS in ART. DYD emerged as a crucial component in the realm of pregnancy care.

Keywords: Progesterone, Micronized, Dydrogesterone, Pregnancy, Infertility

INTRODUCTION

Progesterone is crucial for the female reproductive cycle, including menstrual cycle, implantation, and maintenance of pregnancy. During the luteal phase, progesterone is secreted from the corpus luteum and instigates secretory transformation of the endometrium into an implantation-receptive state.[1] Progesterone continues to be produced

during pregnancy, where it is involved in modulating the maternal immune response, reducing uterine contractility, and regulating the utero-placental circulation, thus contributing to the maintenance of pregnancy.[1,2]

Insufficient level of progesterone leads to irregular menstruation, increased endometrial hyperplasia, subsequent risk of endometrial neoplasia, and luteal phase insufficiency which causes decreased fertility, miscarriage, preterm labour, and early pregnancy loss.[1,2] Hence, exogenous progesterone is used to treat various gynaecology and obstetrics conditions associated with reduced progesterone activity.[1,3]

Progestogens widely used in pregnancy include dydrogesterone (DYD), natural progesterone, and 17a-hydroxyprogesterone caproate (17OHP-C), that can be administered orally, intramuscularly, vaginally, or rectally. Oral natural micronized progesterone (oral NMP) requires multiple daily doses due to first-pass metabolism and is associated with adverse events due to active metabolites.[1] Micronized progesterone administered vaginally provides high uterine bioavailability attributed to the fact that the first pass effect through the liver is bypassed, but few adverse events associated with its use include local irritation, itching, vaginal discharge, and difficult or painful intercourse.[4,5] A sustained-release formulation of NMP (NMP-SR) was later developed to overcome the limitations of oral NMP. NMP-SR has a better tolerability profile than conventional oral NMP and is more bioavailable, allowing for once-daily dosing.[1] Intramuscular (IM) supplementation is important for patients with low progesterone levels undergoing assisted reproductive technology (ART) and gives promising pregnancy results similar to those patients with higher progesterone levels.[6] However, IM progesterone has been associated with significant local pain and discomfort, sterile abscess formation, and inflammatory and allergic reactions to the oil-based vehicle.[5] 17- OHP-C, on the other hand, is only approved for the prevention of recurrent spontaneous preterm birth (PTB).[7] DYD is highly selective for the progesterone receptor and has enhanced oral bioavailability. It is effective in treating reproductive disorders such as threatened abortion (TA) and recurrent pregnancy loss (RPL), and has a good safety and tolerability profile with few side effects, making it the ideal candidate for luteal phase support (LPS) in ART. It has also been described to provide similar reproductive results as vaginal progesterone.[8]

Though progesterone supplements are prescribed for treating progesterone deficiencies in pregnant and infertile women, there is ambiguity on the use of different forms of progesterone supplements prescribed in various conditions, duration, dosing regimen etc. The survey was conducted with the aim to gain insights into the practice profile of Indian gynaecologists on progesterone supplements and the various factors governing these choices.

METHODS

In this cross-sectional survey based study, a pre-designed questionnaire was validated and distributed digitally among gynaecologists across India, with the purpose of understanding the: 1) Usage pattern of different Progesterone preparations (NMP-SR, NMP capsule, DYD) in various gynaecological conditions, as a standalone therapy and combination therapy, 2) Duration, 3) Variation in doctor preferences, 4) Side effects, 5) Considerations and criteria for prescribing any Progesterone supplement, 6) Treatment regimen for PTB, LPS in ART, TA and recurrent abortion (RA).

The survey was conducted from November 2022 to August 2023 following approval by the Institutional Ethics Committee of Anand Multispeciality Hospital, Vadodara, India (Approval number: MA/20/22-Agenda No-052/2022). Informed consent was obtained digitally from all the participating doctors before initiating the survey. Categorical variables were presented in frequencies and percentages. The responses were presented descriptively in tables, and graphical representations were used to visualize where necessary. All statistical analysis was performed through manual excel analysis.

RESULTS

A total of 513 practicing gynaecologists participated in the digital survey. Table 1 summarizes the years of experience of participants at the time of the survey.

Table 1: Summary statistics for doctor profile.

Years of experience	Percentage of participants
<5	7%
6-10	19.3%
11-20	46.4%
21-30	21.1%
31-40	5.1%
41-50	1%
>50	0.2%

In what percentage of patients do you prescribe progesterone supplementations?

In 20-50% patients, 48% and 41.9% Gynaecologists prescribed DYD and NMP-SR, respectively. Whereas 58.5% prescribed NMP vaginal capsule in < 20% patients (Table 2).

Which progesterone supplementation do you prefer the most (in PTB, TA, RA, LPS)?

In PTB, DYD and NMP -SR were preferred by 36.3% each. DYD was preferred by 59.1% as LPS in ART, 74.9% in TA and 69% in RA (Figure 1).

Table 2. Percentage of progesterone supplements prescribed.

Progesterone supplementation		Percentage of patients	Response (%)
Oral	NMP - SR tablet	<20%	30.4%
		20%-50%	41.9%
		>50%	27.7%
	DYD tablet	<20%	23.2%
		20%-50%	48%
		>50%	28.8%
Vaginal	NMP capsule	<20%	58.5%
		20%-50%	24.6%
		>50%	17%

NMP - SR: Natural Micronized Progesterone - Sustained release, DYD: Dydrogesterone, NMP: Natural Micronized Progesterone.

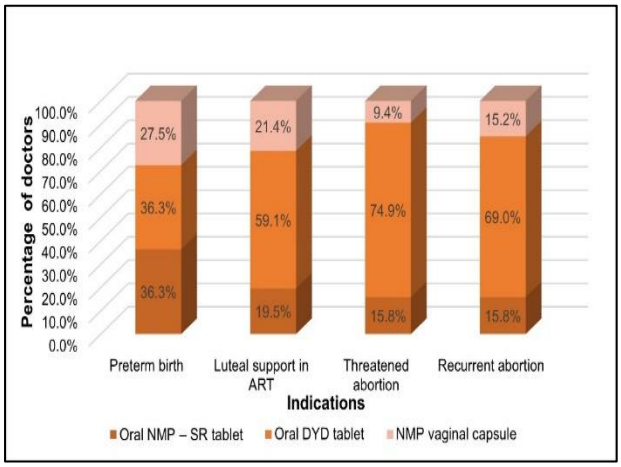

Figure 1: Preferred progesterone supplementation for each indication.

Which progesterone supplementation do you use (in PTB, TA, RA, LPS), at what dose and for what duration?

For PTB

DYD 10 mg twice daily (BID) was preferred by 75.8% Gynaecologists, 10 mg thrice daily (TID) by 17.2%, whereas 7% didn't prefer.

NMP-SR 200 mg BID was preferred by 63.9% Gynaecologists, 300 mg BID by 22.4%, 400 mg BID by 5.8%, whereas 7.8% didn't prefer.

NMP vaginal capsule 200 mg BID was preferred by 62.6% gynaecologists, 400 mg BID by 14.4%, 300 mg BID by 10.1%, whereas 12.9% didn't prefer.

About 49.1% gynaecologists prescribed progesterone supplements up to 34 weeks, whereas 36.8% and 14% prescribed up to 20 weeks and up to 37 weeks, respectively.

For LPS in ART

DYD 10 mg BID was preferred by 74.1% gynaecologists, 10 mg TID by 19.1%, whereas 6.8% didn't prefer.

NMP-SR 200 mg BID was preferred by 54.8% Gynaecologists, 300 mg BID by 14.4%, 400 mg BID by 7.6%, 200 mg TID by 6.4%, 300 mg TID by 2.9%, 400 mg TID by 1.4%, whereas 12.5% didn't prefer.

NMP vaginal capsule 200 mg BID was preferred by 50.3% gynaecologists, 400 mg BID by 10.5%, 300 mg BID by 8.6%, 200 mg TID by 6.2%, 300 mg TID by 2.1%, 400 mg TID by 1.9%, whereas 20.3% didn't prefer.

About 55.2% Gynaecologists prescribed progesterone supplements up to 12-13 weeks, whereas 29.8% and 14.4% prescribed up to 20 weeks and up to 9-10 weeks respectively.

For TA

DYD 10 mg BID was preferred by 65.3% Gynaecologists, 10mg TID by 29.4%, whereas 5.3% didn't prefer.

NMP-SR 200 mg BID was preferred by 56.3% Gynaecologists, 300 mg BID by 16.4%, 200 mg TID by 7.4%, 400 mg BID by 5.1%, 300 mg TID by 2.5%, 400 mg TID by 0.8%, whereas 11.5% didn't prefer.

NMP vaginal capsule 200 mg BID was preferred by 48% gynaecologists, 400 mg BID by 11.5 %, 300 mg BID by 8.8%, 200 mg TID by 6.4%, 400 mg TID by 1.9%, 300 mg TID by 1.6%, whereas 21.8% didn't prefer.

About 46.8% gynaecologists prescribed progesterone supplements up to 12-13 weeks, whereas 39.4% prescribed up to 20 weeks and 13.8% up to 7 days from bleeding episode.

For RA

DYD 10 mg BID was preferred by 70.8% Gynaecologists, 10 mg TID by 25.3%, whereas 3.9% didn't prefer.

NMP-SR 200 mg BID was preferred by 51.5% Gynaecologists, 300 mg BID by 19.7%, 200 mg TID by 8%, 400 mg BID by 5.8%, 300 mg TID by 2.9%, 400mg TID by 1.2%, whereas 10.9% didn't prefer.

NMP vaginal capsule 200 mg BID was preferred by 47.6% Gynaecologists, 400 mg BID by 15%, 300 mg BID by 11.5%, 200 mg TID by 4.3%, 300 mg TID by 1.8%, 400 mg TID by 1.4%, whereas 18.5% didn't prefer.

About 56.1% gynaecologists prescribed progesterone supplements for up to 20 weeks, whereas 26.3% and 17.2% prescribed up to 12 weeks and up to 37 weeks respectively.

What common side effects do you come across with progesterone supplementation?

Common side effects reported with oral progesterone

Drowsiness or giddiness, nausea/vomiting, migraine/headache, and abdominal pain/bloating (Table 3).

Table 3: Side effects reported with oral progesterone.

Side effects	NMP – SR (%)	DYD (%)
Drowsiness or Giddiness	21.5%	15.1%
Nausea/vomiting	20.5%	17.9%
Migraine/headache	14.2%	12.5%
Breast pain/tenderness	14.1%	11.1%
Abdominal pain/bloating	13.6%	13.8%
Vaginal haemorrhage	8.2%	7.9%
NA	6.8%	20.6%
Others	1.1%	1.1%

NMP - SR: Natural Micronized Progesterone - Sustained release, DYD: Dydrogesterone, NA: Not Applicable.

Side effects reported with vaginal progesterone

Vaginal irritation or dryness (28.3%), soreness (13.3%), skin rashes (9.3%), not applicable (9.1%), breast tenderness (8.8%), spotting (8.1%), diarrhoea (7.8%), flatulence (7.6%), somnolence (5.4%) and others (2.2%).

Which factors do you consider before prescribing progesterone supplementation?

The top three factors considered were patient's obstetrics history (26.2%), indication (18.6%) and route of administration/efficacy (12.2% each). The remaining factors were dose (11.1%), cost (8.6%), side effect profile (4.4%), patient choice (3.4%) and age (3.2%).

Do you prescribe progesterone as a combination therapy?

About 67.8% gynaecologists used multiple progesterone preparations in combination and of these 38.7% combined DYD + NMP-SR, 28.2% NMP vaginal capsule + DYD, 21.4% DYD + Injectable, 10.8% NMP-SR + NMP vaginal capsule. The most common condition was TA (29.9%), where combination therapy was prescribed followed by RA (27.5%), LPS in ART (22.4%), and PTB (20.1%).

Which regimens do you practice in TA?

About 43.5% Gynaecologists reported prescribing DYD 40 mg immediately followed by 30 mg/day for 7 days in TA (Figure 2).

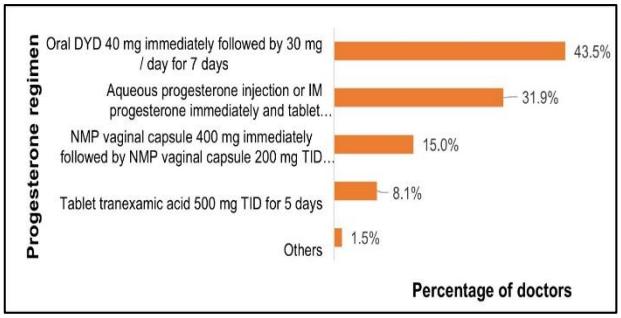

Figure 2: Progesterone regimen used in threatened abortion.

Which therapies are useful to prevent preterm labour in twin pregnancy?

About 35.8% gynaecologists prescribe DYD 10 mg TID to prevent preterm labour in case of twin pregnancy, followed by injection 17-OH progesterone once a week (27.6%) and NMP vaginal capsule 400 mg once a day (19.8%). Lesser prescribed therapies included progesterone + beta agonist (11.3%), nifedipine (4.4%), and others (1.1%; progesterone SR + tocolysis, DYD 10 mg BID, NMP – SR TID).

Do you measure serum progesterone levels before starting progesterone therapy?

About 69.4% do not measure serum progesterone level before starting Progesterone therapy, while only 30.6% measure it beforehand.

DISCUSSION

All 513 gynaecologists surveyed use some form of progesterone supplements in all their patients of TA, PTB, RA, and LPS; <40% Gynaecologists prescribe oral progesterone in 20-50% of patients and 58.5% prescribed NMP vaginal capsule in <20% patients. DYD has been used widely for the treatment of TA, PTB, RA, and as well as for LPS in ART.[9,10] Similarly in our survey >50% Gynaecologists preferred DYD as progesterone supplement for TA, RA, and LPS in ART. However, for PTB, >35% Gynaecologists preferred DYD and NMP-SR equally.

Preterm birth

Progesterone supplementation is one of the options to prevent PTB. Meta-analyses have shown that progesterone is effective in reducing the risk of PTB before 34 weeks.[1] Likewise, in this survey 49.1% Gynaecologists prescribed progesterone supplements up to 34 weeks in PTB. According to the American Congress of Obstetricians and Gynaecologists and The Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines, Vaginal progesterone may be considered to treat PTB but according to SOGC Vaginal progesterone 200 mg daily may be considered to treat PTB.[11,12] In our survey, 62.6%

Gynaecologists preferred 200 mg NMP vaginal capsule BID in PTB.

PTB is a common complication of twin pregnancy and the leading cause of perinatal morbidity and mortality.[13] Vaginal progesterone neither prevents PTB, nor improves perinatal outcomes in twin gestations, but appears to reduce the risk of PTB occurring at early gestational ages and of neonatal morbidity and mortality in twin gestations with a sonographic short cervix.[14] According to SOGC Vaginal progesterone 400 mg daily may be considered to treat PTB.[12] However, in our survey, the use of 10 mg DYD TID by 35.8% Gynaecologists to prevent PTB was observed in twin pregnancies.

Luteal phase support in ART

Exogenous progesterone supplementations have commonly been used for supporting the LPS in ART.[15] Similarly, in this survey, 55.2% Gynaecologists prescribed progesterone supplements up to 12-13 weeks in case of LPS in ART. According to European Society of Human Reproduction and Embryology (ESHRE) guidelines on Controlled Ovarian Stimulation (COS), 200 mg TID NMP vaginal capsule can be prescribed for LPS in ART, while in our survey 50.3% gynaecologists preferred NMP vaginal capsule 200 mg BID. ESHRE - COS and Indian Society for Assisted Reproduction guidelines recommend DYD 30 mg (10 mg TID) for LPS in ART.[16,17] In our survey, 74.1% gynaecologists preferred DYD 10 mg BID.

Many reports have suggested the addition of DYD to vaginal progesterone in LPS.[18-20] However, in our survey, 67.8% gynaecologists used progesterone supplements in combination and of these 37.8% used DYD + NMP-SR.

Recurrent abortion

Progesterone supplementation is often prescribed beginning in the first trimester to prevent spontaneous or recurrent miscarriages.[1] In our survey, about 56.1% gynaecologists prescribed progesterone supplements for up to 20 weeks in RA. According to ESHRE guidelines, DYD and vaginal progesterone are recommended to treat RPL.[21] Similarly, in our survey, 70.8% gynaecologists preferred DYD 10mg BID, and with NMP vaginal capsule 47.6% gynaecologists preferred 200 mg BID.

Threatened abortion

TA is a common problem encountered during pregnancy that inevitably leads to abortion or continues until the pregnancy reaches maturity. This depends on early diagnosis and appropriate therapeutic management.[22] In our survey, about 46.8% gynaecologists prescribed progesterone supplements for up to 12-13 weeks in TA. A meta-analysis by Zhao et al has shown that DYD is effective in the treatment of TA.[23] In this survey, 65.3% gynaecologists preferred DYD 10mg BID.

In our survey, TA (29.9%) was the most common condition where combination therapy was prescribed.

When asked for regimens prescribed exclusively for TA, 43.5% gynaecologists reported prescribing DYD 40 mg immediately followed by 30 mg/day for 7 days, and 31.9% prescribed aqueous progesterone injection or IM progesterone immediately and tablet tranexamic acid 500 mg TID and DYD 10 mg TID for 7 days.

The top factors for prescribing Progesterone supplements were Patient's obstetrics history, indication, and route of administration/efficacy. The most common adverse events reported in studies with oral progesterone were drowsiness/somnolence, dizziness and nausea and with vaginal progesterone irritation and discharge.[1,24,25] Similarly, in our survey, the most common adverse events reported with oral progesterone were drowsiness or giddiness, nausea/vomiting, while those with vaginal progesterone were vaginal dryness/irritation, soreness and skin rashes.

This was one-of-its-kind study that helped provide insights on the clinical practice of Indian gynaecologists on the use of micronized progesterone and DYD. Numerous published literatures recommend using progestogen supplements from menarche to menopause. Including the use of various progestogens in all gynaecological conditions would have been exhaustive and, hence, was excluded. However, to elicit focused responses, the questions were structured on gaining insights on the use of progesterone supplements only in pregnancy and ART cycles. SR formulation of NMP was launched in India with the aim of improving patient compliance and was not featured in any international guidelines at the time of this study. A major limitation of our study was the smaller sample size. So, a large-scale survey is recommended to yield more generalizable results.

CONCLUSION

This survey provided insights into usage patterns of oral and vaginal Progesterone preparations in PTB, TA, RA, and LPS in ART. It also enabled a deeper understanding of gynaecologists' considerations while using Progesterone preparations in their practice, the doses, and duration of use. In conclusion, the use of Progesterone in pregnancy has been the subject of extensive research and clinical practice. Evidence suggests that Progesterone supplementation can be beneficial in certain clinical situations such as LPS in ART, RPL, TA, and prevention of PTB in women with a history of spontaneous preterm delivery. Progesterone remains a valuable tool in the management of high-risk pregnancies, highlighting the importance of individualized care and close monitoring by healthcare professionals. As research advances and our understanding deepens, progesterone therapy may continue to evolve, potentially offering even greater benefits to maternal and fetal health in the future. Dydrogesterone emerged as a crucial component in the

realm of pregnancy care. Its distinct pharmacological profile, characterized by higher progesterone receptor affinity and minimal androgenic effects, renders it a preferred choice in managing various pregnancy-related conditions. The efficacy of dydrogesterone in supporting pregnancy maintenance and mitigating the risk of miscarriage, especially in cases of RPL and threatened miscarriage, underscores its significance in clinical practice. Its ability to provide progesterone support without significant adverse effects enhances its appeal among healthcare providers.

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