Case Series

Individualized approach to infertility management with dydrogesterone: insights from case series

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ABSTRACT

Infertility is a growing global concern, affecting about one in six individuals of reproductive age. In India, reported prevalence ranges from 3.9% to 16.8%, influenced by age, infections, lifestyle factors, and sociocultural elements. This case series highlights six women, aged 30–34 years, each presenting with different infertility challenges: Tubal factor infertility, male factor infertility, recurrent pregnancy loss, unexplained infertility, and early-stage endometriosis. All cases were managed with a personalized treatment approach that included oral dydrogesterone for luteal phase support (LPS). Dydrogesterone, a selective oral progestin with high bioavailability and endometrial specificity, was used to improve luteal phase adequacy and endometrial receptivity. Each patient received tailored care involving either natural conception support, ovulation induction, intrauterine insemination, or assisted reproductive technology, depending on their clinical profile. Oral dydrogesterone was administered as part of LPS in all six cases. Outcomes included successful conception or sustained pregnancy, demonstrating clinical benefit in each scenario. These real-world clinical cases emphasize the importance of individualized infertility management and illustrate the versatile role of dydrogesterone across varied reproductive conditions. Its incorporation into treatment protocols supported favorable outcomes, reinforcing its value in both spontaneous and assisted conception pathways.

Key words: Dydrogesterone, Endometrial receptivity, Individualized treatment, Infertility, Luteal phase support

Infertility, defined as the inability to achieve pregnancy after 12 months of regular unprotected sexual intercourse, affects millions of individuals globally [1,2]. The prevalence of infertility varies from 3.9% to 16.8% in India. Numerous factors, including age, lifestyle, and sociocultural influences, contribute to infertility [3,4]. Women suffer from infertility mainly due to polycystic ovary syndrome, endometriosis, and tubal factor infertility, which often originate from untreated infections [4]. In men, infertility is reported due to impaired sperm quality and quantity. Underlying issues such as varicoceles become an important part of managing male infertility [4].

Dydrogesterone, a synthetic progestin, is an effective therapy for managing various reproductive disorders in women. By supporting corpus luteum function and improving endometrial receptivity, dydrogesterone plays a crucial role in reducing the risk of miscarriage and enhancing fertility outcomes [5]. Dydrogesterone is formulated for oral intake and has higher bioavailability than oral micronized progesterone and possesses strong immunomodulatory properties [6,7].

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This case series features six profiles, each showcasing unique infertility cases managed with personalized interventions, including oral dydrogesterone for luteal phase support (LPS). Although dydrogesterone is commonly used in fertility treatment, the clinical evidence of its effectiveness across different cases remains limited. Therefore, the report aims to highlight the practical benefits of dydrogesterone as part of tailored infertility therapy, demonstrating its usefulness in both natural and assisted conception scenarios.

CASE SERIES

The case series highlights six women, aged 30–34 years, presenting with diverse fertility challenges. Cases 1, 2, and 5 feature primary infertility due to bilateral tubal blockage, male factor infertility, and unexplained infertility, respectively. Case 3 involves a woman with recurrent pregnancy loss (RPL), whereas Case 4 describes a primigravida with first-trimester bleeding caused by a retrochorionic hematoma. Case 6 focuses on a patient with Stage I–II endometriosis, diagnosed via laparoscopy.

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Diagnostic evaluations were tailored to each case and included hormonal profiling, imaging studies, and male factor assessments, reflecting the multifaceted nature of reproductive health disorders. Patient characteristics and key findings are summarized in Table 1.

Treatment Plan

Oral dydrogesterone was administered across all six cases with individualized duration and timing based on the specific clinical setting. In Case 1 (infertility due to bilateral tubal blockage, managed with *in vitro* fertilization [IVF]) and Case 5 (unexplained infertility managed with IVF), dydrogesterone was administered at a dose of 10 mg thrice daily starting from the day of oocyte retrieval until the day of the serum beta-human chorionic gonadotropin (hCG) test for LPS. In Case 2 (male factor infertility managed with intrauterine insemination [IUI]), a dose of 10 mg thrice daily from the day of the IUI until the day of the serum beta hCG test was prescribed for LPS during her IUI cycle. In Case 3 (RPL), dydrogesterone 10 mg thrice daily was started from the day of ovulation until 12 weeks of gestation to take care of the growing pregnancy and aid immunomodulation. In Case 4 (primigravida with first-trimester bleeding), an initial loading dose of 40 mg dydrogesterone followed by 10 mg thrice daily from the day of admission, continued until 1 week after cessation of bleeding, to help arrest bleeding and aid the growing pregnancy. In Case 6 (early-stage endometriosis post-surgery), dydrogesterone 10 mg thrice daily was prescribed during the post-operative recovery phase to prevent recurrence of endometriosis and support spontaneous conception.

Treatment Outcome

In Case 1, oral dydrogesterone supported the luteal phase during IVF, leading to a successful pregnancy after single blastocyst transfer. In Case 2, the patient received micronutrients and antioxidants alongside dydrogesterone during IUI, with positive results. Case 3 involved recurrent miscarriages managed with folic acid,

Table 1: Patient presentations

Case	Age	Gestational age	Past medical history	Symptoms	General examination	Diagnostic evaluation outcome
1	30	Not pregnant	Multiple cycles of oral ovulogen stimulation	Infertility for 6 years	Unremarkable	Bilateral blocked fallopian tubes (HSG); Right tube: middle one-third; Left tube: cornual end; six oocytes aspirated; two Grade A blastocysts obtained on Day 5
2	33	Not pregnant	Six cycles of ovulation induction with clomiphene	Infertility for 4 years	Normal in the female partner; bilateral Grade 2 varicoceles in the male partner	Patent fallopian tubes (HSG); normal baseline hormonal profile (female); male factor infertility (oligoasthenoteratozospermia: sperm count 6.8 million/cmm, 10–20% motility, 98% abnormal forms)
3	32	Not pregnant	Three miscarriages in 5 years, non-consanguineous marriage	Recurrent first-trimester miscarriages	Normal	Normal investigations; normal karyotype of abortus; APLA panel, Factor V Leiden mutation, and parental karyotype all normal; 3D ultrasound and office hysteroscopy normal
4	33	First trimester	Primigravida, conceived after oral ovulogens and timed intercourse	Sudden onset of bleeding per vaginam	Normal general examination	Normal baseline hormonal profile; patent fallopian tubes (HSG); normal semen analysis (partner); large retrochorionic hematoma on ultrasound
5	32	Not pregnant	Married for 4 years, 3 years of treatment for infertility	Anxious to conceive, infertility for 3 years	Normal general examination	Normal HSG, hormonal profile, male partner semen analysis; normal uterine cavity and patent fallopian tubes (hysterolaparoscopy); failed IUI cycles; ovarian reserve evaluation and male DNA fragmentation testing led to the diagnosis of unexplained infertility
6	34	Not pregnant	Married for 3 years, abdominal pain for 6 months	Abdominal pain (premenstrual and 1st day of menses), infertility concerns	Normal uterine cavity and endometrium	Normal ovaries and fallopian tubes, Stage I-II early endometriosis diagnosed at hysterolaparoscopy; powder black burns and red wine deposits at uterosacral ligaments and cul-de-sac; treated with bipolar fulguration and lavage

HSG: Hysterosalpingography, IVF: *In vitro* fertilization, APLA: Antiphospholipid antibody, IUI: Intrauterine insemination, DNA: Deoxyribonucleic acid, Semen analysis: Analysis of sperm count, motility, and morphology, Fulguration: Cauterization technique used for treating endometriosis, GnRH: Gonadotropin-releasing hormone, hMG: Human menopausal gonadotropin, sperm count – The number of sperm present in a given volume of semen, Grade A Blastocysts – Embryos of the highest quality, ready for implantation

antioxidants, and dydrogesterone, resulting in a viable pregnancy. In Case 4, dydrogesterone was effective in a case of threatened miscarriage with a large hematoma. Case 5 showed success in unexplained infertility with IVF and dydrogesterone support. Case 6 featured early endometriosis treated surgically, followed by dydrogesterone, leading to natural conception.

DISCUSSION

This case series highlights the complex, multifactorial nature of infertility, including tubal, unexplained, and male factor causes. Assisted reproductive technology (ART) with dydrogesterone for LPS played a vital role in management.

Progesterone deficiency is strongly linked to RPL, threatened abortion, and lower success rates in ARTs. LPS is a standard intervention in most ART cycles, as progestins support corpus luteum function and implantation [6]. Dydrogesterone, a stereoisomer of progesterone, has been extensively used for the management of progesterone deficiency-associated infertility. Dydrogesterone, a stereoisomer of progesterone, is used widely for progesterone deficiency-related infertility. Its unique structure improves progesterone receptor selectivity and minimizes interaction with other hormone receptors [8]. A meta-analysis reported oral dydrogesterone increased ongoing pregnancy at 12 weeks (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.08–1.61, p=0.0075) and live birth (OR 1.28, 95% CI 1.04–1.57, p=0.0214) compared to micronized vaginal progesterone (MVP). Supplementation from 6 to 20 weeks also reduced pre-eclampsia risk [9]. Studies show dydrogesterone offers a favorable benefit–risk profile and better tolerability than MVP. Oral administration is often preferred for ease and reduced discomfort [10]. A comparative overview of the present case report with existing literature is shown in Table 2.

Tubal factor infertility accounts for approximately 12% of infertility cases. In such instances, IVF becomes the treatment of choice, especially when ovarian function is intact, bypassing the need for surgical intervention [11]. In our patients, oral dydrogesterone

Table 2: Comparative overview of the present case report with existing literature

Study/reference	Cause of infertility	Treatment approach	Dydrogesterone dose and duration	Outcome	Remarks
Maladkar *et al.* [5]	Multiple indications of infertility and early pregnancy support	Ovulation induction, luteal support, and miscarriage prevention	10–30 mg/day	Improved outcomes in clinical use	Review of therapeutic versatility in reproductive practice
Griesinger *et al*. [6]	Luteal phase support in ART	IVF (multiple studies reviewed)	10–30 mg/day	Effective and better tolerated than vaginal progesterone	Summarized pharmacology, mechanism
Raghupathy and Szekeres-Bartho [7]	Recurrent pregnancy loss	Natural conception	Variable dosing up to 12 weeks of gestation	Modulation of immune tolerance, reduced miscarriage	Highlighted immunomodulatory role of progesterone
Griesinger *et al*. [8]	Luteal phase insufficiency in IVF	IVF (fresh cycles)	30 mg/day (10 mg TID) from oocyte retrieval	Comparable pregnancy rates to vaginal progesterone	Effective higher pregnancy rate and live birth rate
Drakopoulos *et al*. [9]	Luteal phase deficiency	ART cycles	10–30 mg/day	Effective luteal support	Dydrogesterone has a good safety and tolerability profile
Dönmez *et al*. [12]	Unexplained infertility	IUI	10 mg BID from IUI until pregnancy test	Comparable outcomes to vaginal progesterone	Showed oral route as an acceptable alternative in IUI cycles
Tournaye *et al*. [13]	Infertility undergoing IVF	IVF (RCT)	10 mg TID versus micronized vaginal progesterone	Non-inferior efficacy, better tolerability	Phase III RCT confirming dydrogesterone efficacy in IVF
Present case study	Tubal factor, male factor, recurrent pregnancy loss, unexplained infertility, endometriosis	IVF, IUI, natural conception, post-surgery	10 mg TID (with variations); up to 12 weeks or until serum β-hCG test	Conception or sustained pregnancy in all six cases	Demonstrates personalized use across diverse infertility conditions

TID: Three times daily, BID: Twice daily, ART: Assisted reproductive technology, IUI: Intrauterine insemination, IVR: *In vitro* fertilization

10 mg thrice daily proved beneficial for LPS during IVF, resulting in successful pregnancies. This aligns with findings from the Lotus I Phase III trial involving 1034 IVF patients, where oral dydrogesterone 30 mg/day (10 mg 3 times daily) achieved comparable 12-week ongoing pregnancy rates (37.6%) to vaginal micronized progesterone 600 mg/day (33.1%). Similarly, Lotus II confirmed non-inferiority of oral dydrogesterone 30 mg/day versus 8% vaginal progesterone gel (90 mg once daily), with 12-week pregnancy rates of 38.7% and 35.0%, respectively. Both randomized controlled trials (RCTs) concluded that oral dydrogesterone is safe, well-tolerated, and as effective as vaginal progesterone [6]. One major concern with vaginal progesterone is local irritation and discharge, reported in 10.5% of patients using MVP, whereas no such side effects were noted in the dydrogesterone group [12].

When female fertility evaluation is normal, male factor infertility must be considered. Varicocele treatment has been shown to be critical to restore or optimize testicular function. Management in such cases often includes micronutrient and antioxidant therapy, followed by an IUI with ovulation triggered by 10,000 IU of highly purified hCG. Studies have reported higher pregnancy rates in patients when they were given progesterone for LPS after gonadotropin-stimulated IUI [9].

A cohort study comparing vaginal progesterone and oral dydrogesterone for LPS in IUI cycles reported comparable pregnancy outcomes between the two groups [1]. Oral dydrogesterone is frequently preferred due to ease of administration, with 10 mg thrice daily showing promising results in LPS [13]. Dydrogesterone is one of the few progestins considered safe in pregnancy [14]. It reduces the risk of miscarriage in threatened and recurrent miscarriage. A review of eight RCTs found that dydrogesterone significantly reduced miscarriage incidence compared to natural vaginal progesterone [7]. These findings support the use of dydrogesterone 10 mg thrice daily as a reliable option for LPS. In addition, dydrogesterone has been shown to modulate cytokine activity, suppressing those detrimental to pregnancy and promoting a favorable immunological environment. Its supplementation has demonstrated benefits in recurrent miscarriage cases by increasing progesterone-induced blocking factor levels, enhancing interleukins (IL)-4 and IL-10 production, and shifting the Th1/Th2 balance in favor of pregnancy maintenance [8]. An initial oral dose of 40 mg dydrogesterone is the recommended treatment in women, followed by a maintenance dose of up to 40 mg/day (20 mg twice daily). This regimen is advised to continue until the 37th week of gestation [14]. As demonstrated in our patient case, oral dydrogesterone also benefits unexplained infertility, failed IUI cycles, and endometriosis-related infertility, with symptom relief and better outcomes [12].

CONCLUSION

The widespread use of dydrogesterone has improved the management of high-risk pregnancies, offering distinct advantages in prenatal care. Its unique structure enhances oral bioavailability over natural progesterone, enabling effective oral use. Clinical trials support its efficacy and safety in treating miscarriage and providing LPS. These cases highlight the importance of accurate diagnosis, individualized treatment, and appropriate luteal support. The use of oral dydrogesterone aligns with modern clinical practices aimed at optimizing pregnancy outcomes across varied infertility scenarios.

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