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Research Article

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Dydrogesterone is Superior as Luteal Phase Support in selected Previously Failed In-Vitro Fertilisation and Embryo Transfer Patients

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Abstract

Different forms of exogenous progesterone have been seen to play a very important role in endometrial maturity. Implantation failure appears to be a significant factor in Assisted reproductive technique (ART) procedures. Even a mature endometrium becomes non-receptive, preventing implantation or rejection of implanted embryo in early months of pregnancy. Hence natural micronized progesterone (NMP) and dydrogesterone have been used since decades to improve endometrial maturity and receptivity. The aim of this study was to investigate causes of failed implantation inspite of uneventful Grade I embryo transfer in ART procedure and the role of natural micronized progesterone (NMP) and dydrogesterone for endometrial maturation. 80 women aged range between 25-40 yr old who visited Department of Reproductive Medicine at Calcutta Fertility Mission, over a period of 24 months (January 2017 to December 2019), satisfying the inclusion criteria, were enrolled in this retrospective observational study. Endometrial aspirate histopathology was done during the secretory phase. They were treated with natural micronized progesterone (NMP) or oral dydrogesterone and results of endometrial changes, clinical pregnancy rate, live birth rate and miscarriage rate were statistically analysed.

26.25% and 29.6% of women were seen to have mid-secretory changes of the endometrium after being treated with NMP in one cycle and dydrogesterone in the subsequent cycle, respectively. 62.71% of women had shown early-secretory changes with dydrogesterone which was statistically significant compared to those treated with NMP (p value=0.006).8.5% of these women showed persistent non-secretory endometrium with either of these medications. The Clinical Pregnancy Rate (CPR) was 38.1% and 47% in the group of patients who were treated with NMP and dydrogesterone respectively. Though pregnancy rate was slightly higher in dydrogesterone group, it was not statistically significant (p value = 0.578). 28.5% and 41% women had live births and 9.5% and 5.8% of them had miscarriage in NMP and dydrogesterone group, respectively, though our data appears to be statistically not significant (p value –0.415) (p value – 0.679). In our study 26.25% women had mid-secretory endometrium after treatment with NMP. 29.6% and 62.71% of these women who had non-secretory or early secretory endometrial changes on treatment with intravaginal NMP, showed endometrial mid-secretory and early-secretory changes respectively, on treatment with dydrogesterone, which implies that oral dydrogesterone is superior to NMP when administered for endometrial maturation in selected patients. Clinical pregnancy rate, live birth rate or miscarriage rate were similar with either NMP or dydrogesterone.

Keywords: In-vitro fertilisation, Implantation failure, Midsecretory endometrium, Natural micronized progesterone, Dydrogesterone, Clinical pregnancy

Introduction

With the gradual popularisation of Assisted reproductive techniques (ART) procedures, new interest has developed about implantation. It has been observed that signs of implantation is very important factor about the success or failure of ART. Large number of failures following the above procedure where fertilised

egg transferred to hormonally prepared endometrial cavity fail to implant leading to loss of pregnancy. This may be due to embryonic defect, that is defective egg or sperm, or deficiency in the receptivity of the endometrium. [1,2]. In treatment of In-vitro fertilisation (IVF) and embryo transfer, there has been a Cochrane review that oral dydrogesterone may be a more effective option than progesterone. Recently, large Phase III developmental programme like Lotus I and Lotus II studies, have also approved oral dydrogesterone for luteal phase support in IVF–ART [3]. Studies were conducted in over 2000 patients and had demonstrated that oral dydrogesterone was of equal efficacy to micronized vaginal progesterone (MVP) capsules or gel for luteal phase support in fresh-cycle IVF, as well in early pregnancy. In our ART practise, IVF failure cases have dictated us to find out the endometrial factor responsible for such implantation failure and choose the correct combination of medication for adequate endometrial maturation [4, 5]. Women with failed In-vitro fertilisation and embryo transfer (IVF-ET) were treated with intravaginal natural micronized progesterone(NMP) and oral dydrogesterone for endometrial maturation. They were assessed with endometrial histopathology and results were analysed. The Clinical Pregnancy Rate(CPR), live birth rate (LBR) and miscarriage rates were also studied and oral dydrogesterone was found to be non-inferior.

Material and Method

80 women who had IVF-ET failure after initial embryo transfer were selected for the study. These women had Day 3 good quality embryo transfer but had failed to achieve pregnancy. They were investigated for endometrial defect for implantation failure. They were aged between 25-40 yr old, with essentially regular and normal menstrual cycles, who visited Department of Reproductive Medicine at Calcutta Fertility Mission, over a period of 24 months (January 2017 to December 2019), were enrolled in this retrospective observational study. Women with diagnosed Polycystic ovarian syndrome, endometriosis, uterine leiomyoma or septate or subseptate uterus, any metabolic disorder were excluded.

In the initial cycle, following IVF failure, when no medications were given, endometrial aspirate (EA) was taken on day 22- day 23 by simple sterile intrauterine insemination (IUI) catheter. It was introduced through the external os and cervix and endometrium was aspirated with a 10ml syringe, with up and down, side by side movement. It was an out-patient procedure without anaesthesia, and care was taken not to cause any discomfort to the patient. Histopathology findings along with integrin were studied. On basis of the histopathology reports patients were given estradiol valerate (4mg) from Day 5 to Day 25 of cycle, with natural micronized progesterone (NMP) (400mg per vagina/day), after serial monitoring of endometrial thickness (by Transvaginal ultrasound) ranging from 8mm to 12mm. They were re-assessed in a similar manner after the medication. The same procedure was repeated in selected group of women (59 women) who failed to show mid-secretory endometrial changes, who were further treated with oral dydrogesterone (20mg/day) instead of NMP. Similar quality embryo was transferred in the subsequent cycle, after pituitary downregulation and hormone replacement was given as combination of oestrogen and progesterone, mimicking the similar one with which we had obtained mid-secretory endometrium, in respective patients.

Ethics Statement

The investigation was performed and medications were given with approval from the Research Ethics Board of the Institute (code: CFM/2019/041) and informed consent was obtained from all study participants.

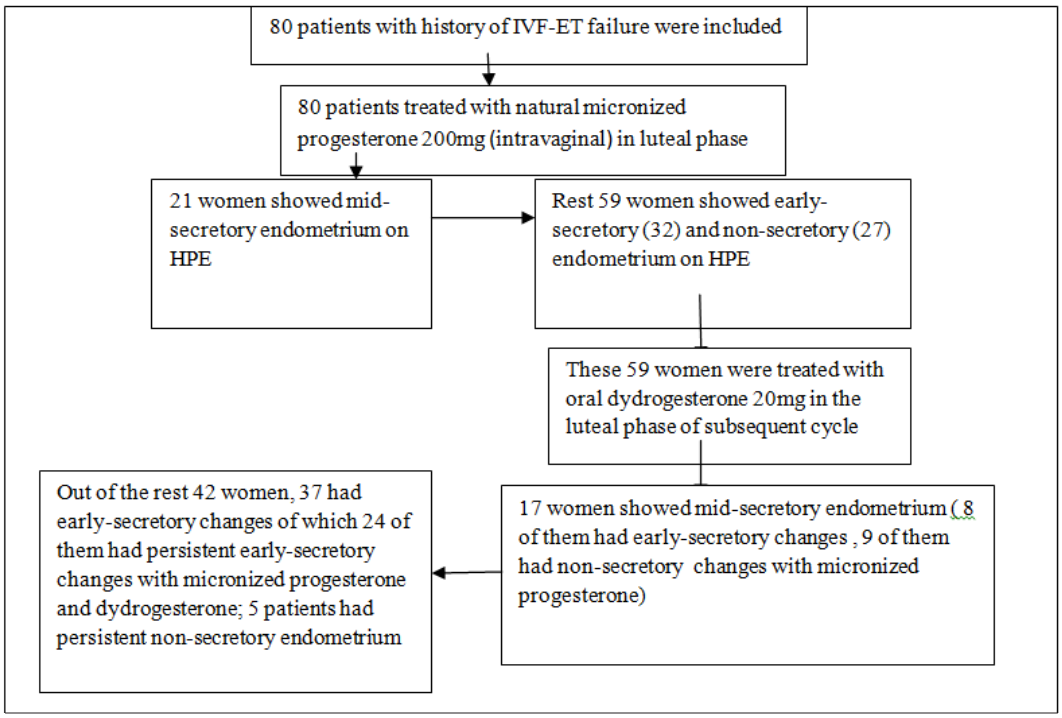

Figure 1: Flow chart of patient selection and endometrial histopathology changes with NMP and dydrogesterone

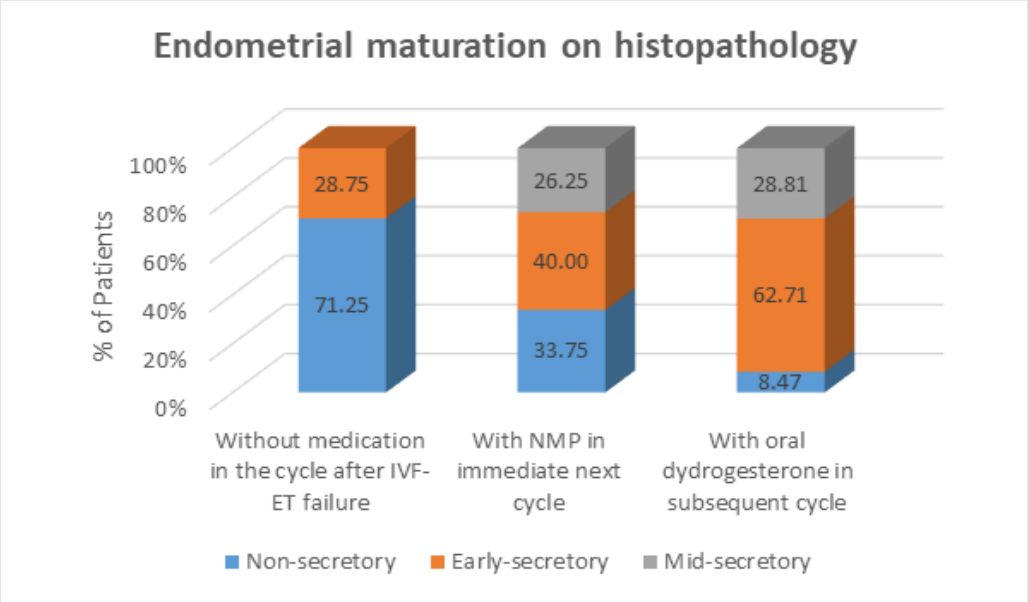

Figure 2: Endometrial maturation on histopathology in 80 women with no medications and with NMP or dydrogesterone in subsequent cycles

Statistical Methods

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant

Table 1: Age of patients

		GROUP			
		NMP	Dydrogesterone	p Value	Significance
AGE	25-30	31(38.75)	21(35.59)	0.845	Not Significant
	31-35	30(37.5)	25(42.37)		
	36-40	19(23.75)	13(22.03)		
Total		80(100)	59(100)		

Pearson's Chi Square test for Independence of Attributes

Table 2: Endometrial changes with NMP and Dydrogesterone in same patients in subsequent cycles

Endometrial changes on histopathology	NMP in initial cycle in 80 women	21 Women With mid-secretory change excluded	Dydrogesterone in subsequent cycle in rest 59 women	p Value	Significance
MID-SECRETORY	21/80 (26.25%)		17/59(29.6%)	0.738	Not Significant
EARLY-SECRETORY	32/80 (40%)		37/59 (62.71%) *	0.006	Significant
NON-SECRETORY	27/80 (33.75%)		5/59 (8.5%) **	<0.001	Significant

*24 women had persistent early secretory endometrial change with either NMP or Dydrogesterone and 13 of them showed early secretory changes from non-secretory endometrium with dydrogesterone

**5 women had persistent non-secretory endometrial change with either NMP or Dydrogesterone

Data presented as n %; Pearson's Chi Square test for Independence of Attributes

Table 3: Comparison of CPR, LBR and Miscarriage rate in women treated with NMP and dydrogesterone in IVF-ET

	NMP	Dydrogesterone	p Value	Significance
CLINICAL PREGNANCY RATE*	8/21(38.1%)	8/17(47%)	0.578	Not Significant
LIVE BIRTH RATE*	6/21(28.5%)	7/17(41%)	0.415	Not Significant
MISCARRIAGE RATE#	2/21 (9.5%)	1/17(5.8%)	0.679	Not Significant

Data presented as n %;
* Pearson's Chi Square test for Independence of Attributes # Fisher's Exact Test

Discussion

Progesterone changes proliferative endometrium to secretory endometrium. The expression of endometrial receptors for estrogens and progesterone varies during the various phases of the physiological menstrual cycle. Progesterone induces secretory transformation and has immunomodulatory effect inhibiting tissue rejection, blocks the chemokines-transcription factor, leading to decreased prostaglandin synthesis & release positively regulating PIBF (Progesterone Induced Blocking Factor), on estrogen primed endometrium [6-8].

Only progesterone, dydrogesterone and 17α-hydroxyprogesterone caproate, however, are currently approved for clinical use during pregnancy [9]

We have considered using vaginal NMP for endometrial maturation in our patients, as it has been accepted to be quite beneficial in the literature. The morphology of the endometrium has been studied and compared after oral, vaginal or intramuscular administration of progesterone, by C. Bourgain et al., and findings were correlated with the serum levels of 17-β oestradiol, progesterone and the pregnancies obtained after oocyte donation. After vaginal application of micronized progesterone, endometrial morphology closely matched that of a natural cycle, which also had supported two ongoing pregnancies. Endometrial maturation was noted to be inadequate after oral ingestion or intramuscular injections of progesterone and hence vaginal route for administering micronized progesterone was concluded to be the treatment of choice in patients without ovarian function. NMP vaginal insert seems to be an effective method of providing progesterone to the endometrium. It has been seen to be superior to oral progesterone tablets and vaginal gel (single application), and is more effective at the endometrial level with less side effects. Though it does not appear to be more effective than intramuscular progesterone injection, despite attaining a higher endometrial concentration in the endometrium, with fewer side effects. [10, 11]

There has been extensive debate on the issue of the choice of molecule and mode of progesterone administration to provide greatest benefit to the patients undergoing IVF-ET. According to Tomic Vet al., vaginal bleeding, interference with coitus and local adverse side effects such as vaginal irritation and discharge occurred significantly more in vaginal gel group [12].

The extensive first-pass metabolism of oral progesterone limits its efficacy and high doses may increase the risk of intrahepatic cholestasis in predisposed cohort of women. To stave off these issues, the different routes of administration of progesterone, for luteal phase support during IVF till quite some time, have been intravaginal, subcutaneous and intramuscular [13, 14]. Dydrogesterone, an oral retrosteroid with unique molecular features creating a 'bent' conformation with enhanced rigidity, with a greater bioavailability, and higher selectivity for the progesterone receptors, at a relatively lower dose, has been proved to have similar efficacy as of micronized vaginal progesterone (MVP) for the treatment of threatened and recurrent miscarriage, and infertility due to luteal phase insufficiency [13, 15, 17-19]. Several authors in previous literature have mentioned that oral dydrogesterone is as efficacious as MVP for luteal phase support, but there is still dilemma on the non-inferiority [20-25].

Oral dydrogesterone (30mg) has been used for luteal phase support on an empirical basis since the early days of in vitro fertilization (IVF) treatment. Given the widespread preference of women for an oral compound, dydrogesterone has been well accepted as the new standard for luteal phase support in fresh embryo transfer IVF cycles and it has firmly established similar role as micronized progesterone for luteal phase support. Lotus I study has also demonstrated that a 20-fold lower dose of oral dydrogesterone (30 mg) is non-inferior to micronized vaginal progesterone (600 mg) for luteal phase support, and is also borderline advantageous in successful pregnancies and consequent live births [26]. Lotus I and Lotus II further stated that oral dydrogesterone and micronized vaginal progesterone, had comparable safety and tolerability profiles, overall incidence of congenital, familial and genetic disorders were also similar [4,5]

In our study we had noted a unique feature about oral dydrogesterone. Patients who had IVF-ET failure and had undergone endometrial biopsy after being treated with NMP, were prescribed oral dydrogesterone (20mg/day) along with estradiol valerate(4mg) for the next cycle, depending on the histopathology reports. A recent meta-analysis was conducted in studies that used fresh or artificial frozen-thawed IVF protocols [27]. however, the clinical heterogeneity that may occur due to the endocrinological differences between fresh and artificial frozen-thawed IVF protocols, has not been considered and Cochrane Database Review 2017 has also not shown any preference for any single regimen compared to the other. Hence in the present study we have used these medications irrespective of the cycle regimen pattern [28].

It is quite evident from the present data that 29.6% patients who did not respond to NMP eventually showed mid-secretory endometrial maturation with dydrogesterone, though the data was not

statistically significant (p value = 0.738). In almost 40% women endometrium remained early-secretory in NMP group, but 62.71% of these women showed early-secretory endometrial changes on administering oral dydrogesterone; which has been analysed to be statistically significant (p value=0.006). It may be due to defective absorption of the drug, inadequate dose building of oral hormones or a defect in concentration or development of the endometrium or endometrial receptivity defect. 33.75% of women showed non-secretory endometrium with NMP, whereas only 8.5% patients had shown persistent non-secretory changes on treatment with dydrogesterone. The data has been seen to be statistically significant (p value<0.001), which proves oral dydrogesterone is more efficacious than vaginal NMP, when used for endometrial maturation (Table 2).

Microarray analysis of endometrial tissue, genomic and proteomic analyses, mass spectroscopy and chromatography assessing levels of PGE2 and PGF2α, aspiration and assessment of secreted uterine fluids, called secretomics, during the secretory phase, that utilize high-throughput techniques with sophisticated large data analysis to generate detailed patterns of molecular and biochemical processes, has revolutionized our understanding of the receptive endometrium. [29-32].

Moreover, due to the structural differences with progesterone, neither dydrogesterone or dihydrogesterone can be quantified by any commonly used diagnostic test for measuring progesterone levels, and hence we did not have any serum estimation to detect the hormone level. Considering the dose related issue regarding inability of endometrial maturation further study is being performed [33].

The Clinical Pregnancy Rate (CPR) was 38.1% and 47% in the group of patients who were treated with NMP and dydrogesterone respectively (p value = 0.578) (Table 3). Our results are in correlation with the study by Chakravarty B.N et al., where both these drugs were seen to have similar efficacy in successful pregnancies. Live birth rate in the group of patients who were given NMP and dydrogesterone were 28.5% and 41% respectively [20]. Though the present data appears to be statistically not significant, (p value –0.415), still we can conclude that NMP and oral Dydrogesterone are similar in yielding live birth (Table 3). Griesinger G et al., had even suggested in a recent study that oral dydrogesterone was associated with a significantly higher ongoing pregnancy rate and live birth rate than MVP administered as capsules or as a gel. [34].

Good quality evidence indicates that oral dydrogesterone provided similar results as vaginal progesterone capsules on live birth or ongoing pregnancy. Additionally, moderate quality evidence suggests there is no relevant difference on usage of these two drugs on miscarriage rates. In a study by Hee Joong Lee et al., it has been stated that oral dydrogesterone, may effectively prevent miscarriages in pregnant women with threatened abortion [35]. Although the number, scale, and methodological quality of the eligible studies limit the significance of their meta-analysis results, these results have been considered to be important. The present study shows miscarriage rate was 9.5% and 5.8% in NMP and dydrogesterone groups, respectively (p value- 0.679) (Table 3) [36].

Conclusion

In our study although 26.25% women had mid-secretory endometrium after treatment with NMP, almost 70% of them had either early-secretory or persistent non-secretory endometrium. 29.6%, 62.71% of these women who had non-secretory or early secretory endometrial changes on treatment with intravaginal NMP, showed endometrial mid-secretory and early-secretory changes respectively, on treatment with dydrogesterone, which implies that oral dydrogesterone is superior to NMP when administered for endometrial maturation in selected patients.

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