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Research article

OPEN-LABEL OBSERVATIONAL STUDY TO DETERMINE THE SUCCESS RATE OF FIRST CYCLE INTRA UTERINE INSEMINATION (IUI) INVOLVING LUTEAL PHASE SUPPORT WITH ORAL NATURAL OR SYNTHETIC PROGESTERONE

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ABSTRACT

IUI has been associated with a pregnancy rate of 10–20% per patient, with wide variation, especially in patients undergoing super ovulation for unexplained infertility, female age and amount of motile sperm while receiving adequate luteal phase support. The current study was planned as an epidemiological survey to determine the success rate of IUI when supported with oral natural or synthetic progesterone. Consecutive sixty IUI cycles in women with unexplained infertility were evaluated for serum progesterone levels while assessing the pregnancy rates following the insemination procedure. Patients received either oral natural micronized progesterone sustained release or synthetic progestin (Dydrogesterone) formulation once or twice a day respectively for two to four weeks till the next menses. Pregnancy was confirmed by urinary & biochemical investigation. Three (5%) cases had pregnancy at the first IUI cycle. Sr. Progesterone levels were maintained at ≥14 ng/ml for 56 (93.3%) patients during the mid-luteal phase. There were no side effects reported during the luteal phase administration of oral progesterone. The pregnancy rates could be related to strategy for monofollicular development, first cycle assessment and trend for a lower motile fraction noted in the current study.

Key words: Intrauterine Insemination, Unexplained infertility, Dydrogesterone, Oral natural micronized progesterone sustained release

INTRODUCTION

Intrauterine insemination (IUI) is often used for the management of infertility presenting with various causes, including cervical factor, ovulatory dysfunction, endometriosis, immunological causes, male factor and unexplained infertility. IUI is generally considered to be an intermediate step before application of sophisticated assisted reproductive techniques like In-vitro Fertilization (IVF-ET) or Intracytoplasmic Sperm Injection (ICSI).

The overall success rate of IUI remains controversial with pregnancy rates in the range of 10%-20% (per cycle), and cumulative pregnancy rates are in the 30%-45% range[1]. The pregnancy or delivery rates are often confounded by several factors, including superovulation for unexplained infertility, female age and amount of motile sperm while receiving adequate luteal phase support[2].

Following IUI, progesterone is usually supplemented during the luteal phase to facilitate better implantation of the embryo and sustenance in the ART of pregnancy. In such cases, oral administration of natural micronized progesterone as sustained

release (SR) preparation offers consistent tissue concentrations for endometrial support offering once a day dosage convenience thereby improving the patient compliance. The slow, sustained release kinetics of progesterone by SR formulation minimizes drug exposure to liver metabolic enzymes at individual time points, thereby offering sustained action with minimal central side effects including Drowsiness due to the active metabolite Allopregnanolone[3].

This observational study was conducted to evaluate the success rate during the first cycle of IUI with luteal phase support involving oral progesterone supplementation.

MATERIALS & METHODS

This open label, prospective, observational study was conducted in the out-patient department of Sooriya Hospital, Chennai with approval from an Independent Ethics Committee and written informed consent from the patients. The study is registered with Central Trial Registry India (CTRI/2014/02/004407). Sixty women with unexplained infertility aged >18 to 33 years were prospectively enrolled in this observational study between June and November '13. Exclusion criteria included women with a history of Progesterone use in the past three months, tubal insufficiency or obstruction, including Endometriosis or Polycystic Ovarian Syndrome, psychoactive disease or on antidepressants, smoking, myocardial infarction, stroke, cardiovascular/circulatory or clotting disorders; AST and / or ALT > 2.5 x ULN, Serum creatinine > 1.5 mg/dl. Women with Uncontrolled hypertension, hypercholesterolemia or diabetes, Women on oral anticoagulants or prolonged use of high doses of NSAIDs and those are hypersensitive to natural micronized progesterone or Dydrogesterone.

At the first visit, detailed history, physical examination and medications of the subjects were recorded. They were, then, subjected to IUI procedure. Subsequent to IUI procedure, oral progesterone, including natural micronized progesterone and Dydrogesterone supplement was prescribed for 4 weeks. Dose administered was as per prescribing information sheet information for respective formulations. IUI was conducted using natural or stimulation protocol as deemed appropriate by the Investigator. The stimulation protocol included Clomiphene citrate with/without HMG injection. Tablet Clomiphene citrate 100 mg was started from day 2 of menstrual cycle for 5 days with Inj HMG 75 IU being administered on alternate days from day 5. Inj Human chorionic gonadotropin (HCG) 5000 IU was administered intramuscularly with IUI procedure within the next 48 hrs. Following IUI procedure, on day 22+/-1, the serum progesterone levels were assessed following administration of either Dydrogesterone (10 mg bid) or oral NMP sustained release preparation (400 mg once a day at bedtime) for four weeks. In case of missed menses, patients were requested for urinary pregnancy test for further confirmation by biochemical investigation.

RESULTS

Prospectively 60 patients with unexplained infertility were observed. The baseline demographics are presented in Table 1.

Table 1: Baseline demographics of 60 patients

Characteristics	N= 60
Mean age	28.3 yrs
Mean Height	160.2 cms
Mean Weight	62.25 kg
Obstetric History (Mean)	
G	0.2
P	0.08
A	0.1
L	0.05
Menstrual Cycle	
< 3 days	1
3 days	38
> 3 days	21

The serum progesterone levels were calculated at Day 23 and are presented in Table 2 and Fig. 1

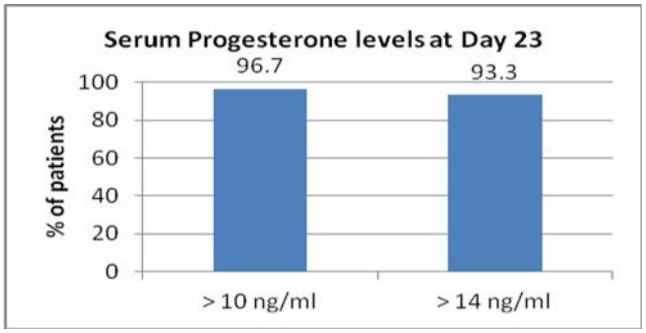

Fig. 1: Serum Progesterone levels of 60 patients

Table 2: Serum Progesterone levels of 60 patients

Sr. Progesterone levels	Patients (%)
≥ 10 ng/ml	96.7
≥ 14 ng/ml	93.3

Comparison of Serum Progesterone levels in Natural Progesterone and Dydrogesterone presented in and Fig. 2. Table 3 and Table 4 show Serum Progesterone levels in Natural and artificial progesterone respectively.

Table 3: Serum Progesterone levels in Natural progesterone

Serum Progesterone Levels	Natural Progesterone (n= 30)
≥ 10 ng/ml	93.3 %
≥ 14 ng/ml	90 %

Table 4: Serum Progesterone levels in synthetic progesterone

Serum Progesterone Levels	Dydrogesterone (n= 30)
≥ 10 ng/ml	100 %
≥ 14 ng/ml	96.7 %

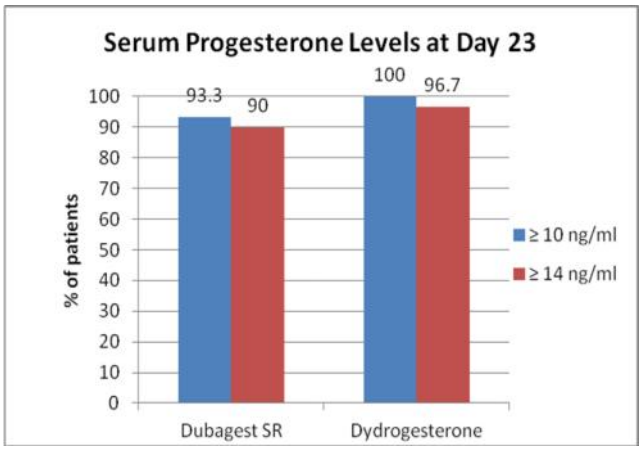

Fig 2: Comparison of Serum Progesterone levels in Natural progesterone and Dydrogesterone

The mean serum progesterone achieved in the both groups were 46.2 and 51.7 ng/ml for oral NMP sustained release preparation and Dydrogesterone respectively, with no significant difference between the levels achieved ($p>0.05$). The overall pregnancy rate was 5% (3/60). Out of these 2 pregnancies were reported in patients who were administered natural micronized progesterone and 1 pregnancy was reported in patients with Dydrogesterone.

DISCUSSION

For the right candidate, IUI is usually a successful, easy, and a safe infertility treatment option preceded by natural or stimulation protocol. Multiple factors need to be assessed when deciding about the choice of treatment. The patient's age, the duration of infertility, ovarian function, etiology of infertility, semen characteristics, the status of the tubes, and the presence of other gynecologic or medical problems all have to be considered. The two most important benefits of IUI are the simplicity of the treatment and the low cost[4]. The reported pregnancy rates per cycle range from 8 to 22%. Several prognostic factors have been incriminated in determining the success rate of IUI procedure and include factors like patient's obstetric history, duration or type of infertility, presence of stimulation protocol, follicular monitoring, endometrial thickness, and timing of IUI and semen parameters like post wash motility, morphology and total motile fraction

The current study was conducted as an open-label, observational, surveillance study to assess the success rate of IUI procedure for the first cycle while determining the concomitant prognostic or confounding variables including serum progesterone levels achieved during the Luteal phase with oral supplementation

We obtained a pregnancy rate for the first cycle as 5% (3/60). No major congenital anomaly was recorded nor were there any multiple pregnancies. Several factors could probably explain lower pregnancy rates in our setting, including monofollicular development with Natural cycle, first cycle assessment and trend for a lower motile fraction. In recommending treatment options, clinicians usually weigh several factors, including treatment cost, feasibility and compliance of patients to treatment strategies or monitoring protocols and patient profile. Natural IUI offers complimentary yet comprehensive evidence of ovarian hyperstimulation and high-order multiple pregnancies avoidance. A combined analysis of the literature on unexplained infertility yielded estimated pregnancy rates of 4 percent per cycle for Natural IUI cycles, 8 per cent per cycle for superovulation cycles, and 18 per cent per cycle for Stimulated IUI cycles. Although to the best of our knowledge, there have been no previous large-scale, randomized comparisons between

Natural and stimulated IUI cycles, a randomized trial conducted highlighted significantly higher birth rates (5.6 times higher) with superovulation and intrauterine insemination compared with no treatment among women with minimal or mild endometriosis[5,6]. The current study evaluated the success rate for the first cycle of IUI since available literature suggests relatively constant rates for the first three to seven cycles[7, 8].

Similarly, during the LPS, serum progesterone levels to achieve for the continued sustenance of pregnancy are ideally ≥14 ng/ml[9]. Around 93.3% of the patients achieved these levels with no significant differences between the groups receiving natural or synthetic progesterone i.e. Dydrogesterone. Oral natural micronized progesterone as 400 mg sustained release formulation was administered for once a day administered at bedtime. The formulation was well tolerated with none of the patients reporting central side effects, including drowsiness the next day

This study represents one of the first clinical trial to evaluate the success rate of IUI procedure using oral natural progesterone as Luteal phase support after Pouly et al (1996)[10] reported 29.9% PR with IVF-ET following oral micronized progesterone administration of 300 mg/day in divided dosages.

The study was limited was a small sample size that was observational in nature and needs to be explored further within a larger, randomized clinical trial settings to further evaluate the likely confounding variables that may explain the success rate of IUI procedure especially the natural cycles without stimulation protocol. The study was further exploratory in nature trying to determine also the close relationship of serum progesterone levels achieved with oral progesterone supplement administered as LPS and may need to be again evaluated for Cumulative success or pregnancy rate for confirmation of this association

CONCLUSION

Natural IUI represents an important treatment option for women with unexplained infertility, especially when female age is <35 years. The Low pregnancy rate observed during the first cycle of evaluation may not be related with therapeutic levels achieved with oral natural or synthetic progesterone supplements

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Conflict of Interest – None

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