RESEARCH ARTICLE

Gonadotropins combined with and without 100mg Clomiphene Citrate drug on ovulation induction and role of epidural analgesia in pregnancy outcome of infertility women

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ABSTRACT

Successful ovulation induction can overcome the common condition of infertility associated with ovulatory dysfunction. Monotherapy of clomiphene citrate (CC) or combined with gonadotrophins are the best treatment modalities for ovulation induction with a successful outcome. We concentrated on evaluating the effects of 100 mg Clomiphene Citrate, both with and without gonadotrophins, on ovulation induction and the outcome of labor analgesia in women with infertility. This prospective cohort consists of 136 women with infertility who were medicated with 100 mg of clomiphene citrate alone and 100 mg of clomiphene citrate with gonadotropins. We recorded the endometrial thickness, details of the dominant follicle, and the incidence of a positive pregnancy rate. Women with positive pregnancy were managed with epidural labor with labor analgesia to relieve labor pain and evaluated the foetal outcome. In CC alone, the ovulation rate was 57%, while in CC with gonadotrophins, it was 81%. The mean dominant follicle size and endometrial thickness were high in CC with gonadotrophins ($p<0.05$). The overall incidence of positive pregnancies was 28.98%. Levobupivacaine with dexmedetomidine significantly reduced the mean VAS score from baseline, resulting in a higher foetal body weight. Taking 100 mg of Clomiphene citrate with gonadotropins works better than taking Clomiphene citrate by itself at starting ovulation, increasing the size of the dominant follicle, and improving the thickness of the endometrium. With levobupivacaine plus dexmedetomidine, the labor analgesia showed better stability in hemodynamic parameters and effective control on labor pain scores.

Keywords: Ovulation induction, Infertility, 100 mg clomiphene citrate, Labor analgesia.

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INTRODUCTION

Ovulatory dysfunction is the commonly encountered reproductive failure in the infertile and sub-fertile people.[1] Ovulation induction is frequently used modality to manage infertility in anovulation even in unexplained infertility. It enhances the production of dominant follicle by acting as estrogen receptor antagonist or by direct stimulation of hypothalamus through gonadotrophins.[2,3]

Clomiphene citrate, a nonsteroidal triphenylethylene derivative and selective estrogen receptor modulator commonly used to induce ovulation in people with anovulatory or oligo-ovulatory infertility.[4] Combining gonadotropins with Clomiphene citrate reduces the necessary dosage for optimal stimulation and increases cost-effectiveness in women who do not react to CC therapy.[5] However, efficacy of gonadotrophins alone, Clomiphene citrate alone or combined with gonadotrophins in the management of infertility is still controvertible.

The epidural analgesia is frequently used for labor pain relief. Even though, studies reported that it has drawbacks in terms of hypotension, motor blockade and prolonged second stage labor.[6] Dexmedetomidine is an alpha-2 adrenergic agonist is an effective adjuvant with notable sedative and analgesic properties that reduces the local anaesthetics requirement with minimal side effects.[7,8]

There is literature lack in the outcome of Clomiphene citrate alone or combined with gonadotrophins in the management of ovulation induction in infertility and anaesthetic management of cases had positive pregnancy and role of labor analgesia in the pain management of women undergone infertility

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treatment. Hence, this study was focused to assess the Clomiphene Citrate 100mg with and without gonadotrophins on ovulation induction in infertility women.

MATERIALS AND METHODS

The current prospective follow up study was carried out at the Department of Obstetrics and Gynaecology in collaboration with the Department of Anaesthesiology at Apollo Institute of Medical Sciences, Hyderabad, from June 2022 to June 2024. A cohort of 136 women, aged 21-35 years, who were receiving outpatient care in the obstetrics and gynaecology department, were enlisted for the study.

Inclusion and Exclusion

Participants included individuals who experienced infertility, had unobstructed fallopian tubes on both sides, engaged in frequent unprotected sexual intercourse for a duration exceeding one year, had normal results in semen analysis, had normal pelvic anatomy, had no prior history of receiving external gonadotropin therapy, were considered and included. In exclusion, cases with infertility with an immunological cause, early ovarian failure, uterine and ovarian cysts, surgical history related to the genital tract, cardiovascular and renal problems, hyperprolactinemia, and those who were not willing to participate. All research participants provided written informed permission, and the study procedure was approved by the institutional ethics committee.

Management of infertility

All participants were randomly allocated to two study groups. Group 1 consists of 68 participants undergone ovulation induced medication (100mg of clomiphene citrate) on 3rd day to 7th day of menstrual cycle. Group 2 with 68 participants undergone ovulation induced medication with add on gonadotrophins (100mg of clomiphene citrate + gonadotrophins). Participants were undergone hysterosalpingography to diagnose the malformations of uterus and transvaginal USG to identity the follicle size and number, and endometrial thickness. When individuals ceased menstruating, laboratory tests were done, including a urine pregnancy test (UPT) and an ultrasound (USG) with necessary laboratory investigations.

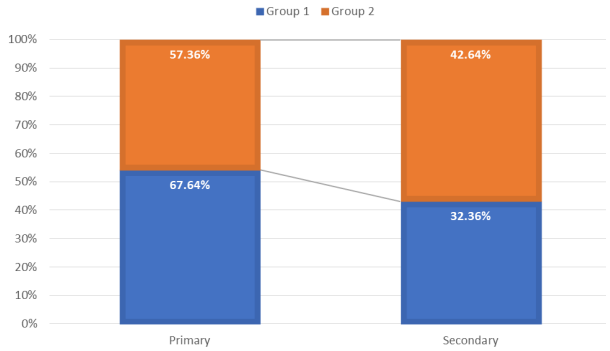
Anaesthetic management

After infertility management, forty women with positive pregnancy (n=16 in group 1 & n=24 in group 2) were randomly allocated to two study group. Group 1 participants were managed with 0.125% of levobupivacaine + dexmedetomidine (0.5mcg/kg) and group 2 participants were not given any form of pain relief medication. Maternal blood pressure, heart rate, and pain score by VAS are monitored. Onset of analgesia, sensory and motor blockade, cervical dilation, duration of labour, foetal heart rate, and APGAR score were recorded.

Collected data was assessed by SPSS version 26.0. Data was expressed as mean, standard deviation. Comparison of data was performed by using unpaired t test, one way ANOVA and chi square test. The p-value <0.05 was considered as statistically significant outcome.

Table 1: Clinico-Demographic profile of women with infertility.

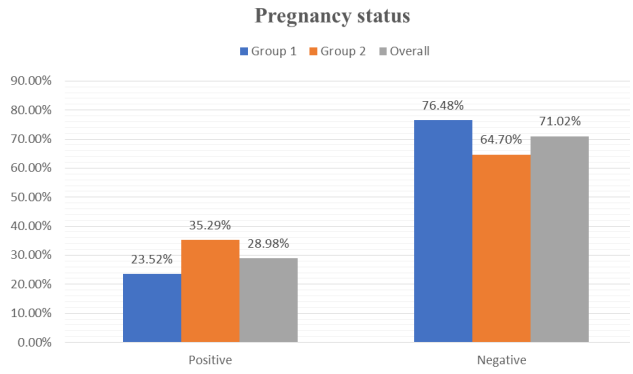
Demographic profile	Group 1 (n=68)	Group 2 (n=68)
Age	24.8±3.17	25.7±2.29
Height	154.5±4.77	156.43±4.82
Weight	63.8±7.24	65.12±10.02
BMI (Kg/m^2)	25.89±4.67	26.42±2.18
Occupation		
House wives	37 (54.41%)	40 (58.82%)
Semiskilled	06 (8.82%)	05 (7.35%)
Skilled	12 (17.64%)	11 (16.17%)
Professionals	13 (19.11%)	12 (17.64%)
Marital period		
Below 4 years	33 (48.52%)	27 (39.70%)
Above 4 years	35 (51.48%)	41 (60.30%)
Regular Menstrual status	24 (35.29%)	26 (38.23%)
+Ve PCOS	26 (38.23%)	28 (41.17%)



Graph 1: Type of infertility among study participants

Table 2: Comparison ovulation induction outcome between study groups

Parameter	*Group 1*	*Group 2*	*One way ANOVA*	*p-value*
Dominant follicle size	17.84 ±3.05	20.04 ± 2.95	3.01	0.001
Endometrial thickness	7.22 ± 7.67	8.11 ± 5.44	12.28	0.001



Graph 2: Incidence of pregnancy rate

Table 3: Status of hemodynamic parameters and VAS score of study participants.

Parameter	*Group 1*	*Group 2*	*p-value*
SBP	118.5±7.32	118.9±6.18	1.82
DBP	71.59±2.75	73.37±3.16	0.742
Heart rate	78.6±3.22	79.4±2.98	0.210
Oxygen saturation	98.86±5.90	99.67±8.02	0.426
VAS score			
Baseline	7.98±1.12	8.11±1.48	0.001
At 30 min	3.98±0.71	8.37±0.95	0.001
At 1 hour	1.58±0.56	8.26±1.04	0.001
At 2 hours	1.53±0.92	8.40±0.77	0.001
At 3 hours	1.57±0.67	8.29±1.28	0.001

Table 4: Fetomaternal outcome.

Parameter	*Group 1 (n=20)*	*Group 2 (n=20)*	*p-value*
Mode of delivery			
LSCS	04 (20%)	02 (10%)	1.380
NVD	16 (80%)	18 (90%)	
Instrumental	-	-	
CTG abnormality			
Late deceleration	01 (5%)	02 (10%)	0.472
without abnormality	19 (95%)	18 (90%)	
Weight of foetus (In kg)	2.81±1.14	2.76±0.93	0.178
APGAR score			
At 1 min	7.5±0.36	7.6±0.61	0.541
At 5 min	8.2±0.84	8.3±0.58	0.076

RESULTS

DISCUSSION

Clomiphene citrate is the primary treatment for anovulation and ovulating women with inadequate follicular or luteal development. The importance of clomiphene in ovarian stimulation for various assisted reproductive techniques is limited since the administration of gonadotrophins yields a more favourable ovarian response.[9] We randomly assigned participants between the ages of 21 and 35 to two groups, with a mean age of 24.8 years in group 1 and 25.7 in group 2. The mean BMI in group 1 was 25.89 kg/m2, whereas in group 2 it was 26.42 kg/m2. 35.29% of individuals in group 1 and 38.23% of cases in group 2 observed regular menstrual periods. PCOS was detected in 38.23% of group 1 and 41.17% of group 2 participants (Table 1). 67.64% of group 1 and 57.36% of group 2 reported primary infertility, while 32.36% and 42.64% of individuals in groups 1 and 2 reported secondary infertility, respectively (Graph 1). The ovulation rate was 57% in group 1 and 81% in group 2. The mean dominant follicle size and endometrial thickness were statistically significant ($p<0.05$) (Table 2). We recorded incidence of positive pregnancy in 23.52% of cases in group 1 and 35.29% in group 2. The overall incidence of positive pregnancies was 40 (28.98%) in both study groups (Graph 2).

A retrospective analysis by Sinha et al., on 100 couples found out 95.91% of ovulation rate and 18.36% of positive pregnancies in clomiphene citrate with gonadotrophins, but better endometrial thickness was observed in cases managed with gonadotrophins alone.[10] Clomiphene citrate is effective in ovulation induction in approximately 80% of subjects who fit for the treatment. because ovulation induction rate was influenced by the age, and BMI.[11] Similarly, our study demonstrated effective outcome in cases managed with clomiphene citrate with gonadotrophins in terms of dominant follicular size, better endometrial thickness, and dominant follicular count than clomiphene citrate alone.

The mean SBP, DBP, heart rate, and oxygen saturation was comparatively low in group 1 ($p>0.05$). The mean VAS score in group 1 was significantly reduced from baseline to 3 hours of procedure. Whereas in groups 2, the mean VAS score was comparatively similar from the baseline to 3 hours of the procedure ($p<0.05$) (Table 3). Normal vaginal delivery was common in both groups and similar APGAR score was observed between the study groups. The weight of the foetus was comparative high in group 1 than group 2 (Table 4).

According to Kabi S et al., on 44 primi parturients, the VAS scores in both groups decreased to less than 3 within 15 minutes. There were significant differences at 5, 10, 15, and 120 minutes, with the 0.125% levobupivacaine + dexmedetomidine group scoring worse overall. In both groups, hemodynamic measures declined markedly from their baseline. Group A saw a much quicker fall in heart rate, and the 0.125% levobupivacaine with dexmedetomidine group had lower diastolic blood pressure (DBP) at practically all-time intervals after baseline. There was no noticeable difference between the two groups in terms of instrumental delivery and caesarean sections in newborns with Apgar scores.[12]

In our study, the mean systolic blood pressure, diastolic blood pressure, mean heart rate, and mean oxygen saturation score were comparatively lower in group 1 than group 2, with a lesser incidence of adverse events. Participants who received dexmedetomidine showed low mean arterial pressure and mean heart rate, according to Afandy ME et al.,[13] but they also experienced a high incidence of bradycardia and hypotension. A few studies reported similar findings, observing no significant difference between study groups managed with levobupivacaine and dexmedetomidine.[14-16] Further studies should focus on multiple drugs as monotherapy or with adjuncts in the management of infertility.

CONCLUSION

The combination of Clomiphene citrate with gonadotropins is more effective in inducing ovulation, higher dominant follicle size, and better endometrial thickness than Clomiphene citrate alone ($p<0.05$). The overall positive pregnancy rate was 28.98%. With levobupivacaine plus dexmedetomidine,

the labor analgesia showed better stability in hemodynamic parameters, effective control on labor pain scores, high foetal birth weight, and a better mean APGAR score.

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