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Original Research Article

## Comparative study between intrauterine insemination following preovulatory perturbation versus intrauterine insemination alone in induced ovulation cycles in infertility patients

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### ABSTRACT

**Background:** To compare the efficacy of perturbation with low dose lignocaine before ovulation followed by intrauterine insemination versus intrauterine insemination alone in induced ovulation cycles in infertility patients.

**Methods:** Total 60 ovulation induction cycles were studied, were randomly divided in Group A and Group B of 30 cycles each. Ovulation induction was done with clomiphene citrate / gonadotrophins. Post ovulation IUI was done in both the groups. Additionally, preovulatory perturbation with low dose lignocaine diluted in balanced salt solution was done 10-12 hrs after ovulation trigger in group A. The primary outcome conception (positive urine pregnancy test) in patients were compared between two groups. The secondary outcomes, full term pregnancy, abortion, ectopic pregnancy, procedural pain, infection, haemorrhage, and long term complications were also studied and compared.

**Results:** Pregnancy rate was found to be slightly more in the preovulatory perturbation with low dose lignocaine and IUI group (20.6% in Group A) as compared to IUI alone group (14.7% in Group B). But the difference was not found to be statistically significant ( $p > 0.05$ ). The spontaneous pregnancy rates in patients with endometriosis is  $< 5\%$ . In the intervention group it was 37.5% in cases with endometriosis, which was encouraging. The perturbation treatment used in this study proved to be a safe treatment option without complications. Procedure was associated with mild to moderate pain in 76% patients and severe in 8.8% patients and one patient (2.9%) had syncope. Post procedure PID was noted in one patient (2.9%).

**Conclusions:** Preovulatory perturbation followed by IUI was associated with increased clinical pregnancy rate as compared with IUI alone in induced ovulation cycles. The efficacy was more pronounced in the patients with endometriosis. It is safe and well tolerated.

**Keywords:** Lignocaine, Infertility, Preovulatory perturbation, IUI, Ovulation induction

### INTRODUCTION

Ovulation Induction and Intrauterine Insemination is the recommended first line treatment for subfertility, borderline male factor infertility, early stage endometriosis and unexplained infertility. The rate of conception with IUI is about 16% and the possible facilitating factors being, ensuring ovulation by ovarian stimulation, obtaining good quality sperms, bypassing the cervical

mucus, overcoming ejaculatory dysfunction and timing the IUI with ovulation etc.<sup>1</sup> The combination of perturbation in addition to IUI has been proved to increase the chances of achieving pregnancy in these couples. The effect of perturbation on fertility can be mechanical as well as anti-inflammatory by using substance that inhibit phagocytosis of spermatozoa like lignocaine which contributes to increasing the number of free spermatozoa and maintaining the possibility of fertilizing an oocyte. For

patients with endometriosis and unexplained infertility, treatment with lignocaine might be a means of increasing the chances of conception.<sup>2</sup>

In mid-follicular phase and before ovulation the endometrial glandular lumen of the fallopian tube is narrow and contains some quantity of glandular and membranous material, cytoplasmic debris and cellular fragments<sup>95</sup> (Amso et al).<sup>3</sup> A partial tubal luminal obstruction may also be due to presence of tubal ostium membranes<sup>96</sup> (Coeman et al).<sup>4</sup> So, flushing the fallopian tubes just before IUI has been proved beneficial in increasing the chances of conception as has been evident from post HSG conceptions in infertile couples.

In endometriosis, the cytokine milieu of the peritoneal fluid is toxic for the gametes and thus can be detrimental for the sperm survival, fertilization and implantation of the embryo. So the immunomodulators like lignocaine may help in tackling with this pathology. Tubal flushing with low dose lignocaine has been studied by Edelstam GA, and et al needs to be substantiated to improve the success rates in IUI cycles in the patients with unexplained infertility and endometriosis.<sup>2</sup> In this study, tubal flushing has been claimed to be effective in significantly enhancing pregnancy rates in insemination cycles. An absolute increase in pregnancy rate was 11.7% and relative increase in pregnancy rate was 465% or 4.5 times.<sup>2</sup>

It is suggested that this anti-inflammatory effect of lignocaine is due to stabilization of the cell membrane by prohibiting the increase of Na<sup>+</sup> permeability and by probably interfering with the ATP in the cell membrane. Preovulatory perturbation with lignocaine can be tried in the patients with endometriosis and / or mild mechanical cause of infertility. It can be carried out while couple is in waiting for IVF and this treatment does not alter the success rate of later IVF cycles.<sup>5</sup>

The aim of this study was to compare the efficacy of perturbation with low dose lignocaine before ovulation followed by intrauterine insemination versus intrauterine insemination alone in induced ovulation cycles in infertility patients and to find out whether there was any increase in clinical pregnancy rates with the intervention.

## **METHODS**

This prospective randomized study was conducted at Department of Obstetrics and Gynecology at Command Hospital, Air Force, Bangalore. During the study period of 18 months from August to January the couples with at least one year of primary / secondary infertility. Approval for this study protocol and clearance were obtained from the Ethical Review Committee of Command Hospital Airforce, Bangalore.

Total 68 cycles were studied in couples with primary and secondary infertility that were considered eligible. 34 cycles each in Ovulation Induction- IUI group (Group B)

and ovulation induction - preovulatory perturbation with low dose lignocaine followed by IUI group (Group A) were studied during this period. Sample size was selected after consultation with the statistician using 95 % confidence level and a confidence interval of 10% with an accuracy of 90%.

### ***Inclusion criteria***

Couples with primary and secondary infertility which included: unexplained infertility, mild to minimal endometriosis with normal tubo-ovarian relationship and within six months of laparoscopic electrofulguration, normal tubal factor and normal uterine cavity, candidates with PCOS, mild male factor subfertility with semen count up to 10 million/ml, women with age less than 39 years.

### ***Exclusion criteria***

Abnormal HSG or laparoscopic findings suggestive of pelvic adhesions with altered tubo-ovarian relationship, major mullerian malformations, tubal blockage, cases with bacterial vaginosis, mucopurulent cervicovaginal discharge, pelvic infections, major endocrinological cause for infertility like hypogonadotrophic hypogonadism, primary amenorrhoea, premature ovarian failure, extensive endometriosis, women with age more than 39 years, pelvic pathology like fibroid uterus, ovarian cysts, other male factor contributing to infertility like aspermia, azoospermia, teratozoospermia, obstructive causes etc.

### ***Ovarian stimulation protocol***

Three different protocols were used for ovarian stimulation as indicated depending on follicular response.<sup>1</sup> Clomiphene citrate 100 mg on D2 to D6 of menses Clomiphene citrate and human menopausal gonadotrophin Gonadotrophin step up protocol (HMG 75 IU step up or FSH 75 IU step up 2, 3). Ovarian response i.e. number and size of follicles and endometrial thickness and morphology was monitored with serial transvaginal ultrasound starting from D7 of the cycle. The ovulation trigger with hCG 10000 IU (Inj Chorion) was administered intramuscularly on appropriate day when lead follicle reached 18-22 mm in diameter. The treatment cycles were cancelled when no dominant follicle was seen by day 14 of the cycle. Tab Oestradiol Valerate 2 mg (Progynova) was given in selected patients with poor endometrial response.

### ***Randomization***

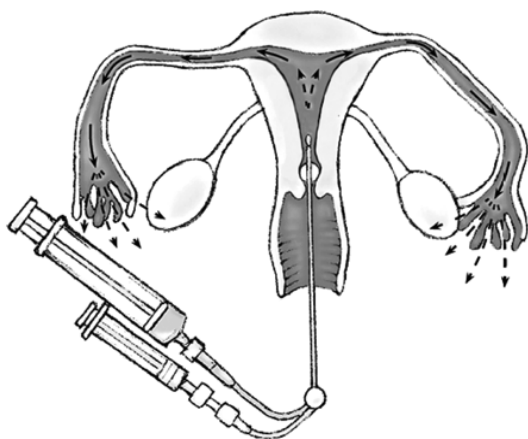
Candidates were randomized on the day of HCG administration according to their serial number. Even numbers were allocated to pre ovulatory perturbation with low dose lignocaine group (group A) and odd numbers were allocated to ovulation induction and IUI group (group B) after obtaining appropriate consent.

### ***Perturbation***

The pertubation procedure (Figure 1) was carried out in the candidates in Group A after confirming absence of mucopurulent cervico-vaginal discharge. Atropine was given intramuscularly in all the patients prior to the procedure. The portio surface was cleaned with saline swab and a pediatric Foley's catheter No 7/8 with the guidewire was inserted just beyond the internal os. The balloon was inflated with 1-2 ml saline for retention of catheter in the cavity and to prevent retrograde leakage. Then the utero-tubal flushing was done with 10 ml of low dose lignocaine solution. No excessive force was used for perturbation procedure, to avoid endometrial injury. Low dose lignocaine solution was produced with 1% lignocaine hydrochloride in a balanced salt solution (0.1 mg Lignocaine /ml)

### **Semen preparation and insemination**

Intrauterine inseminations were carried out in both groups 34-36 hrs after HCG administration. Collection of semen was done a few hours before insemination by standard procedure and after 2-3 days of abstinence. Sperm wash was done by swim up technique. Inseminations were performed with semen preparations containing post swim up  $>10 \times 10^5$  motile spermatozoa by standard technique using Sims or Cusco's vaginal speculum. The vulva, vagina and cervix were gently cleaned with normal saline solution and IUI was performed using a IUI cannula filled with 0.3 to 0.5 ml inseminate. All women remained in supine position for 20 to 30 minutes following insemination. Single insemination was considered for each patient in the study group to avoid bias. One to two complete treatment cycles were offered to each couple. Urine HCG positivity in pertubation and non pertubation group were recorded in absence of menstruation after 7 days of missed periods and clinical pregnancies were recorded subsequently. The adverse effects of pertubation were noted in the pertubation group.



**Figure 1: Pertubation procedure.**

### **Types of outcome measures**

Number of biochemical pregnancies, i.e., urine pregnancy test positivity, number of clinical pregnancies (tubal and ongoing) diagnosed by appearance of gestational sac on ultrasound examination, number of multiple pregnancies, number of abortions, number of tubal pregnancies, number of cycles with ovarian hyperstimulation syndrome, number of procedure (pertubation) related complications. i.e., severe procedural pain, syncopal attack, failure to complete the procedure, allergic reaction to the drug used, number of post pertubation genital infections.

### **Statistical analysis**

For the calculation of significance of the primary outcome parameter, chi-square tests for the comparison of two proportions from independent samples were used. The number of patients needed for significance was calculated assuming a pregnancy rate of 16% in the control group and a pregnancy rate of 30% in a lignocaine-pertubation group, based on earlier clinical study results published by Edelstam et al. The calculations were based on chi-square approximation. The number of participating patients obtained reached a power of 65%. Results are expressed as mean $\pm$ SD range and number and percentages. Student's t-test was used for comparing means of two groups. Chi-Square test was used for analyzing categorical data.  $P < 0.05$  was considered for statistical significance.

Total 98 cases were assessed for the eligibility for the inclusion in the study and were explained about the study, the intervention and its possible immediate and long term side effects. 83 women consented for the participation. Randomization was done as described earlier and 43 cases were allocated to Group A i.e. perturbation and IUI group and 40 were allocated to Group B i.e. only IUI group. 9 cases from Group A and 6 from Group B were excluded from final analysis as either they were lost to follow up or the protocol was discontinued due to various reasons. 3 cases out of these 9 were excluded due to failure to perform the procedure. The reason for failure were non co-operative patient in 1 and difficult cervical negotiation in 2 cases. Overall, 34 cases were finally analyzed in each group as per the protocol.

### **RESULTS**

The patients' mean age was  $29.03 \pm 4.12$  years in Group A and  $28.25 \pm 3.53$  years in Group B. Majority of the cases in Group A i.e. 16 (47.1%) and Group B i.e. 18 (52.94%) were between the age group of 26-30 years. Minimum age was 21 years and maximum age was 38 years. ( $p=0.26$ , the difference was not statistically significant). There were no other demographic differences between Group A and Group B. Also, there were no significant differences in body mass index, type of infertility or mean duration of infertility.

The primary and secondary infertility cases in Group A were 61.8 % and 38.2 % respectively and 58.8% and 41.2% in Group B respectively ( $p=0.804$ , the difference

was not significant). Maximum number of cases in both the groups belonged to 2 to 5 years of duration of infertility. Shortest duration was 2 years and the longest duration was 15 years of infertility.

**Table 1: Distribution of cases by reason for infertility.**

Female factor	Group A		Group B	
	N	%	N	%
<b>Unexplained</b>	8	23.5	13	38.3
<b>Ovulatory dysfunction</b>	11	32.4	11	32.4
<b>Endocrinological cause</b>	7	20.6	6	17.6
<b>Endometriosis</b>	5	14.7	3	8.8
<b>Endometriosis and ovulatory dysfunction</b>	3	8.8	1	2.9
<b>Total</b>	34	100	34	100
Male Factor	Group A		Group B	
	n	%	N	%
<b>Normal</b>	29	85.3	28	82.4
<b>Oligo and/or asthenospermia</b>	5	14.7	6	17.6
<b>Total</b>	34	100	34	100

**Table 2: Distribution of subjects by pregnancy outcome.**

Pregnancy outcome	Group A		Group B	
	N	%	n	%
<b>Live birth</b>	5	14.7	4	11.8
<b>Anembryonic gestation</b>	0	0.0	1	2.9
<b>Spontaneous abortion</b>	1	2.9	0	0.0
<b>Ectopic pregnancy</b>	1	2.9	0	0.0
<b>Total</b>	7	20.6	5	14.7

There were no significant differences between male factors in two groups. In Group A 14.7 % (n=5) male partners had oligo and/or asthenospermia versus 17.6 % (n=6) in Group B (Chi square=0.06, and p=0.804). After sperm preparation, mean sperm count in men in Group A was 54.8 million and average motility was 56.14%, in group B mean sperm count was 51.06 million and average motility was 49.84%.

The ovarian stimulation was carried out with Tab Clomiphene citrate in 82.4% (n=28) cases in group A and 85.3% (n=29) cases in Group B. 17.6 % (n=6) cases were stimulated with combination or gonadotrophin protocol in Group A and 14.7% (n=5) in Group B.

In both group A and group B 8.82 % (n=3) cases developed polyfollicular response to ovulation induction and all of them were stimulated with either combination protocol or gonadotrophins. One of these cases in group B developed mild secondary OHSS with clomiphene citrate which resolved at 10 weeks period of gestation.

The mean number of follicles during the treated cycles did not differ significantly, with 1.65 in the group A as compared with 1.54 in Group B. The mean diameter of follicles was 1.91 in Group A versus 1.88 in Group B and the difference was not statistically significant. The mean endometrial thickness was 8.2 mm in Group A and 7.9 mm in Group B. This too was not statistically significant.

Out of 34 patients in perturbation group, no procedure related pain was recorded in 4 cases (11.8%) Mild to moderate pain recorded in 26 cases (76.4%) and severe pain with or without syncope was recorded in 4 i.e. 11.8% cases. No post procedure short term or remote complications were noted in 28 cases i.e. in 82.4% cases. However, significant abdominal pain persisting for 3-4 days was observed in 1 subject. Spotting was observed in 3 i.e. in 8.8% cases. Pelvic inflammatory disease and vaginosis was recorded in one case each. No cases of post procedure fever, allergic reactions, excessive bleeding P/V were noted in the intervention group. Finally, there were no significant differences in blood pressure or heart rate before and after perturbation.

**Follow up**

Urine pregnancy test was done in all these patients after 7 days of missed period or 21 days after IUI. All cases with UPT positivity underwent TVS for confirmation of intrauterine gestation. Intrauterine gestation was confirmed in all patients with UPT positivity except 1 in Group A who was detected to have an ectopic gestation on serial serum B hCG reports. This patient was managed medically with single dose of Inj Methotrexate.

Primary outcome i.e. clinical pregnancy rate: Pregnancy rate was found to be slightly more in the preovulatory perturbation with low dose lignocaine and IUI group (Group A) as compared to IUI alone group (Group B) in patients with infertility (20.6% versus 14.7% respectively). But the difference was not found to be statistically significant (Chi Square=0.405, df=1, p=0.5245).

In Group A, take home baby rate was 14.7% (n=5) versus 11.8% (n=4) in Group B. There was one case of spontaneous abortion and one case of ectopic pregnancy in group A. (2.9%) occurred in the same group versus one case (2.9%) of anembryonic pregnancy in Group B.

The pregnancies noted in the participants was encouraging but not conclusive enough to draw any definitive conclusion. In Group A, out of 8 patients of endometriosis 3 conceived after lignocaine perturbation and the rate of conception in this subgroup was 37.5% which was very encouraging as the spontaneous pregnancy rates in patients with endometriosis is found to be <5%. The relative increase in clinical pregnancy rate in Group A was 123% with the Odd's ratio 1.23%.

## DISCUSSION

Ovulation Induction and Intrauterine Insemination is often tried as the first treatment for the couples with unexplained infertility, male infertility, and immunologic causes for infertility. It also improves outcomes in patients with anovulatory infertility. The rate of conception with IUI is about 16%.<sup>6</sup> The success rate of ovulation induction and IUI cycles is substantially lower than IVF cycles which is approximately 35%. However, the former is less invasive, can be carried out at a substantially lower cost and does not require sophisticated lab set up. This intervention was focused on evaluating the adjuvant effect of perturbation with low dose lignocaine on the insemination success rate.

For couples undergoing an infertility investigation, Johnson et al in 2005 studied Hystero salpingo contrast sonography (HyCoSy) in infertile couples with unexplained infertility. The procedure consists of a tubal flushing which resulted in an increased pregnancy rate during the following months.<sup>7</sup> When hystero-salpingography (HSG) was performed as an X-ray, there were two different contrast options: an oil-based medium or a water-soluble medium. The pregnancy rate after using the oil-based contrast medium has resulted in twice as many pregnancies compared with a water-soluble medium.<sup>8</sup> In addition, in vitro studies of the oil-based contrast medium lipiodol have shown a reduction of sperm phagocytosis.<sup>9</sup> Tubal flushing with lipiodol has been tried in a small, randomized clinical study on women with endometriosis and no spontaneous pregnancy for 3 years.<sup>10</sup> After perturbation with lipiodol, 30% of the patients achieved pregnancy compared with none of the patients randomized to expectancy. Compared with an oil-based contrast medium which can remain intraperitoneally, a local anaesthetic such as lignocaine has the same capacity in vitro to reduce sperm phagocytosis and is a well-tolerated drug.<sup>11</sup> Perturbation with lignocaine (0.1 mg/ml) in a balanced salt solution was tried in a previous clinical study with the same overall pregnancy rate as was described with lipiodol.<sup>12</sup> No complications were noted with low-dose lignocaine perturbations and no reproductive toxicological problems have been described.<sup>13</sup>

It has been hypothesized that there are more leucocytes in peritoneal fluid in patients with endometrial peritoneal implants and is considered an ongoing sterile inflammation. These leucocytes constitute in vivo primed macrophages which secrete a macrophage derived growth factor (MGDF) and this may explain the proliferation of endometrial tissue.<sup>14-16</sup> Other secretory products from macrophages, growth factors such as tumor necrosis factor (TNF) and interferon exhibit gamete toxicity and may have an adverse effect on fertility process.<sup>17</sup> Such peritoneal fluid significantly reduces the capacity of fimbriae to pick up the fertilized ovum. Also the progressive velocity of spermatozoa is lower in peritoneal fluid from the patients with endometriosis and unexplained infertility.<sup>19</sup>

In similar study conducted by Edelstam et al, clinical pregnancy rate was 14.9% in perturbation group versus 3.2% in group without perturbation.<sup>2</sup> Take home baby rate was 14 % in intervention group compared with 3% in control group. An absolute increase in pregnancy rate was 11.7% and relative increase was 465% or 4.5 times in pertubated patient which was statistically significant. Whereas our study clinical pregnancy rate was found to be slightly more in perturbation group as compared with no perturbation group (20.6% versus 14.7% respectively). But the difference was not found to be statistically significant. Take home baby rate was 14.7% in perturbation group versus 11.8% in control group in our study with an absolute increase by 123%.

Lignocaine is a common local anesthetic and antiarrhythmic drug. Lidocaine alters signal conduction in neurons by blocking the fast voltage gated sodium (Na<sup>+</sup>) channels (VGSC) in the neuronal cell membrane, leading to its anaesthetic effects. VGSC play a role in macrophage function and VGSC blockers impair both phagocytosis and inflammatory responses. Several VGSC blockers have shown immunomodulatory properties in mice models, skewing the immune response toward a Th2- mediated response, while suppressing Th1-mediated responses and may find clinical application in the treatment of autoimmune and inflammatory diseases.<sup>20</sup> Lignocaine is known to have anti-inflammatory effect and has been under trial for use in other specialites as immunomodulator. A study by UteshevS et al on Lidocaine as an immunomodulator in a toxic liver lesion, lignocaine appeared to have induced immunosuppressive properties in red blood cells.<sup>21</sup> Lignocaine is found to be safe in pregnancy. Ramazzotto hypothesized that lignocaine has been used for many years without any reports of adverse effects during pregnancy as has also been studied in an animal study and it should therefore be possible to use lignocaine for the treatment of infertility in the endometriotic patients.<sup>22</sup> This understanding is important for justifying the concept of preovulatory tubal flushing with low dose lignocaine.

This study highlights a new treatment concept based on previously observed increased fertility after HSG. The effect of adding tubal flushing/ perturbation with lignocaine during an insemination cycle is presumed to have two effects: mechanical and immunological. The mechanical effect is thought to be, e.g. opening of loose adhesions around the fimbriae and flushing mucus plugs/ debris which are blocking the tubal lumen.<sup>23</sup> The in vitro observed reduced sperm phagocytosis is presumed also to have an immunological effect in vivo by enhancing the survival rate of spermatozoa.<sup>10,11</sup>

## CONCLUSION

Perturbation with lignocaine is simple and cost-effective intervention which is well tolerated by patients without any serious immediate or remote complications. Pregnancy rate was found to be slightly more in the

preovulatory perturbation with low dose lignocaine and IUI group. However, the difference was not found to be statistically significant ( $p > 0.05$ ). The relative increase (Odds Ratio) in the clinical pregnancy rate was found to be 123%. The pregnancies noted in the participants were encouraging but not conclusive enough to draw any definitive inference. The spontaneous pregnancy rates in patients with endometriosis is  $< 5\%$ . In Group A, out of 8 patients of endometriosis 3 conceived after lignocaine perturbation and the rate of conception in this subgroup was 37.5% which was very encouraging. So far the most effective way of increasing fertility for women with endometriosis or unexplained infertility is in vitro fertilization (IVF). But the perturbation treatment with lignocaine as a novel adjuvant treatment prior to IUI can increase the chances of conception, hence may provide a minimal invasive and more cost-effective alternative to current treatments. Therefore, its efficacy and safety and effects on pregnancy needs to be studied further as limited literature is available on the subject at present.

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