

Improving the pregnancy rates by pre-ovulatory saline perturbation before intrauterine insemination: A prospective randomized controlled trial

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Abstract

Objective: to evaluate effect of pre ovulatory saline flushing on pregnancy rate in patients with ovulatory dysfunction, unexplained infertility, endometriosis and male sub-fertility.

Patients & Methods: the study involved 246 of infertile couples divided blindly by election into two equal group each contain 123; non pertubated group (A) and saline infusion group (B). Controlled ovarian hyper-stimulation by Clomiphene Citrate (100 mg on cycle day 3-7) +HMG (75-150 IU) followed by administration of HCG 5000 IU IM. On the pre-ovulatory day; when one or two follicles >17mm by TVS, tubal flushing with 20 ml saline was carried out in half of the cases (group B).

Results: Patient's demographic data in both groups showed no significant differences, the mean age was 27.8 ± 7.3 and 26.7 ± 8.1 years respectively. The mean weight in Kg \pm SD was 77.1 ± 9.9 and 79.8 ± 10.3 , the mean height in cm \pm SD was 160.5 ± 5.8 and 162.8 ± 7.1 while the duration of infertility in years was 3.4 ± 1.6 and 3.5 ± 1.1 years respectively. The number of follicles reached the maturity in both groups showed no significant difference being 4.43 ± 1.7 and 4.67 ± 1 respectively while the overall pregnancy rate was significantly different in both groups (15/123 = 12.1% in group A and 29/123 = 23.57% in group B and p-value < 0.001). Abnormal pregnancies were more or less similar in both groups (multiple pregnancy, abortion and ectopic occurred in 4, 2 and 1 case of the first while occurred in 5, 4 and 1 case of the second group). Finally the live birth rates was 7.3% (9/123) in group A and 19.5% (24/123) with a significant difference (p value < 0.005).

Conclusion: adding saline flushing to (COH + IUI) cycles can be used as a cost-effective first line treatment for couples with infertility.

Key Words: tubal hydrotubation, infertility, IUI.

Introduction

Infertility is an important problem worldwide. The frequency of infertile couples is suggested to be in a range of 10 – 15% [1]. In approximately one third of the couples, infertility is caused by a male factor, in another third by female factor and in the rest by combined or unexplained factors. For couples with ovulatory dysfunction, early stages endometriosis, unexplained infertility and male sub-fertility, different therapeutic modalities have been proved efficient with various degree of success in achieving pregnancy. These modalities started by controlled ovarian stimulation and timed coitus passing through ovarian stimulation with intrauterine insemination (IUI) or intrauterine insemination alone and ended by IVF or ICSI. The first two modalities are the first choice infertility treatment for the above possible causes. The pregnancy rate per cycle was high using controlled ovarian stimulation (COS) with IUI rather than COS with timed coitus or IUI with non-stimulated cycle [2] (Cochrane Rev., 2006). In spite of being relatively safe and cost-effective, these modalities have lower pregnancy rate per cycle compared with IVF [3].

Hysterosalpingography (HSG) has been claimed to have therapeutic func-

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tion with increased pregnancy rate which may be related to mechanical or immunological effects [4]. Upon these observation, many authors had employed the technique of tubal flushing with significant increased pregnancy rate in stimulated cycles with IUI in couples with unexplained infertility[5,6] and early stages endometriosis [7,8]. Also original used tubal flushing without IUI in cases with mild tubal disease with high degree of success in achieving pregnancy [4].

Tubal flushing could be done as an outpatient procedure and represent easy, less invasive and cost-effective treatment alternative as well as a good trial of achieving pregnancy while being on the list for IVF. Controlled ovarian hyper-stimulation and intrauterine insemination (COH+IUI) remains the first choice treatment for ovulatory dysfunction, unexplained infertility, endometriosis and male sub-fertility[3].

After completed investigation of infertile couples, COH+IUI is often tried as the first line treatment as this increases the livebirth rate compared to IUI alone[2]. Again; tubal Flushing with lipiodol has been tried in a small randomized clinical study on women with endometriosis [7] and evidenced to an innovative treatment for unexplained and endometriosis-related infertility[9] whereas the overall pregnancy rate was 30% at 6 months with no complications[9,10].

In this study, we investigated the effect of pre ovulatory saline flushing on pregnancy rate in patients with ovulatory dysfunction, unexplained infertility, endometriosis and male sub-fertility undergoing intrauterine insemination husband.

Patients and methods

This study was carried out at Fertility Care Unit, Mansoura University Hospital and a private practice setting during the period from June 2011 to October 2013 and comprised of 246 infertile couples undergoing intrauterine insemination (IUI). All patients were diagnosed to have mild male factor, minimal or mild endometriosis or unexplained infertility. All women were <36 years old, normo-ovulatory confirmed by day 21 serum progesterone >5 ng/ml, had patent tubes confirmed by hysterosalpingography and normal laparoscopic findings apart from minimal or mild endometriosis. All semen samples were evaluated according to WHO criteria 2010. The study was approved by the local Institutional Research Ethical Committee and each participant received a brief explanation of the research idea and aim of the work and gave a written consent.

All couples (n=246) were randomly allocated to either study (n=123) or control group (n=123) using computer-generated random table and sealed envelopes. All IUI cycles were preceded by ovarian superovulation with clomiphene citrate 50 mg tablets (Clomid; Hoechst Marion Roussel, Cairo, Egypt, ARE) orally twice daily

for 5 days starting on the second day of the menstrual cycle and one hMG ampoule 75 IU (Menogon; Ferring Pharmaceuticals, Malmo, Sweden) IM daily for 5 days starting day 5 of the cycle. Cycles were monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on days 10, 12, and 14 of the cycle. Human chorionic gonadotropin 5,000 IU injection was given to induce ovulation when at least one follicle measured 18 mm or more.

All semen samples were collected in the laboratory after 3 to 5 days of sexual abstinence. After liquefaction for 30 minutes at room temperature, volume, pH, sperm count, and progressive motility were evaluated according to the WHO standard criteria. Sperm concentration was performed with a hemocytometer on two separate preparations of the semen sample (dilution 1:20 in Ringer's solution). Sperm motility was determined by assessing at least five microscopic fields to classify at least 200 spermatozoa (x4,000 magnification). The motility was graded progressive, non-progressive, or immotile. Motile sperm were selected by a swim-up procedure. In all cases, the motile sperm fraction was washed twice by centrifugation, and the sperm pellet was suspended in 0.35 mL of Earle's balanced salt solution (Sigma-Aldrich Co., Ayrshire, United Kingdom) as a capacitating medium in all patients. After swim up preparation, the IUI was performed with a catheter (The Curve; Medical Systems, Inc., Herts, United Kingdom) 32-36 hours after hCG injection with the total number of motile spermatozoa after preparation more than 5 millions [11]. All patients received 30 mg/day of dydrogesterone (Duphas-ton; Solvay Pharmaceuticals, Hanover, Germany) after insemination till the day of hCG testing. Serum hCG was determined 2 weeks after hCG injection in the absence of menstruation for diagnosis of pregnancy. The outcome measure was the occurrence of clinical pregnancy with TVS performed two weeks later .

Saline flushing was done on the pre-ovulatory day when one or two follicles >17mm were confirmed by trans-vaginal ultrasound. Tubal flushing with 20ml saline by saline flushing procedure was done [12] through cleaning the portio surface with saline swab, inserting and cuffing a foley's catheter (8F) in the cervical canal and finally 20ml saline was injected slowly into the uterine cavity under TVS guidance. The routine use of prophylactic antibiotics was not warranted. After swim-up preparation,

Statistical analysis

All statistical analysis was performed using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean \pm standard deviation (SD). Data were checked for normality and equality of distribution, prior to any analysis being performed. Skewed continuous variables were logarithmically

transformed to attain a normal distribution. For variables that would not attain a normal distribution by logarithmic transformation, nonparametric tests would be used. P-values <0.05 were considered to be of statistical significance.

Result

A total of 246 couples were involved in the study divided blindly into two equal groups each contain 123; non pertubated group (A) and saline infusion group (B). Patient's demographic data in both groups showed no significant differences where the mean age was 27.8 ± 7.3 and 26.7 ± 8.1 years respectively. The mean weight in Kg \pm SD was 77.1 ± 9.9 and 79.8 ± 10.3 , the mean height in cm \pm SD was 160.5 ± 5.8 and 162.8 ± 7.1 while the duration of infertility in years was 3.4 ± 1.6 and 3.5 ± 1.1 years respectively [table 1].

COH and IUI were done for all cases in group A and B, the results obtained and gathered in table [2]. The number of follicles proposed to reach the maturity in both groups showed no significant difference being 4.43 ± 1.7 and 4.67 ± 1 respectively. The overall pregnancy rate was significantly different in both groups ($15/123 = 12.1\%$ in group A and $29/123 = 23.57\%$ in group B and p-value < 0.001). Abnormal pregnancies encountered are more or less similar in both groups as multiple pregnancy, abortion and ectopic occurred in 4,2 and 1 case of the first while occurred in 5,4 and 1 case of the second. Finally the live birth rates registered was 7.3 % (9/123) in group A and 19.5 % (24/123) and there is a significant difference between both (p value < 0.005).

Table (1)

show the demographic data in both groups with no significant difference between them:

Parameter	Group (A): n =123	Group (B): n =123	P value
Mean age (years) \pm SD	27.8 ± 7.3	26.7 ± 8.1	0.17
Weight (kg) \pm SD	77.1 ± 9.9	79.8 ± 10.3	0.018
Height (cm) \pm SD	160.5 ± 5.8	162.8 ± 7.1	0.026
Duration of infertility (years) \pm SD	3.4 ± 1.6	3.5 ± 1.1	0.056
Mean motile spermatozoa before IUI \pm SD	$6.2 \times 10^6 \pm 1.2$	$5.9 \times 10^6 \pm 1.8$	0.035

P value showed no significant difference between both groups in any of the variables.

Table (2)

show the number of follicles measuring > 16 mm in both groups, clinical pregnancy rate and fate of this pregnancy.

Parameter	Group (A): N =123	group (B): n = 123	P value
No. of follicles >16 mm	4.43 ± 1.7	4.67 ± 1	0.043
Clinical pregnancy:	$15/123 = 12.1\%$	$29/123 = 23.57\%$	< 0.001**
Multiple pregnancy	4	5	0.045
Abortion	2	4	0.034
Ectopic	1	1	
Live birth rate	$9/123 (7.3\%)$	$24/123 (19.5\%)$	<0.005*

P value (**) it is highly significant.

Discussion

The present study has approved the treatment concept based on increased fertility after lipiodol flushing and saline infusion sonohysterography where tubal flushing with oil-soluble media (e.g. lipiodol) versus no intervention, was associated with a significant increase in pregnancy rate (OR 3.30, 95% CI 2.00-5.43) as proved by some authors [13]. On the other hand tubal flushing with oil-soluble media was not significantly more effective than tubal flushing with water-soluble media for achieving pregnancy (OR 1.21, 95%CI 0.95-1.54). Here in our research we used only 20 mm³ saline perturbation in the expected pre-ovulatory day after COH and injecting 5000 IU HCG.

Saline flushing may be attributed to enhance pregnancy rates by many presumed effects; mechanical effect by opening of loose adhesions around the fimbriae [14] immunological effects; reducing sperm phagocytosis or enhancing the survival rate of spermatozoa [15, 7] or decreasing levels of toxic peritoneal factors such as cytokines is another proposal effect [16].

The cross talk between embryo and endometrium is found to be enhanced with high implantation rates in IVF following endometrial stimulation [17]. Again, this cross talk between embryo and endometrium after endometrial flushing with embryo culture media the day before embryo transfer increases endometrial receptivity and consequently the pregnancy rates [17]. Such results were achieved in our study where flushing the endometrium and the tubes with non-oil containing fluid "20 mm³ saline" before IUI in 123

cases found to significantly increase the number of pregnancy and live births rates than in the other non pertubated group “p values were <0.001 and < 0.005 respectively”.

On the other hand, Edelstam et al. 2001 [18] demonstrated that a balanced salt solution used for pertubation gave the same overall pregnancy rate as this described with lipiodol. Ramazzotto et al., 1985 [19] reported no complications with low-dose lignocaine pertubations and was well tolerated, the same results were reached by Edelstam et al., 2008 [5] who studied 130 cycles by using 50 mg C.C.+ IUI techniques in a randomized controlled trial by using 1.73 ml lignocaine hydrochloride in a balanced salt solution in 67 cases and saline pertubation in 63 cases and demonstrated that clinical pregnancies in the pertubated group is highly significant compared with non pertubated group ($P < 0.05$) whatever the mode of pertubation.

Importantly, cervical mucus has been reported to have unfavorable effects on pregnancy rates following IVF or ICSI and so cervical mucus aspiration before IUI appeared to lead to significantly increased pregnancy rates [20]. In our research; the increase in pregnancy rate was doubled in pertubated than non pertubated group; this may encourage us to use this procedure on a large scale being a safe treatment option, well tolerated, an office procedure, and assists in the diagnosis with significant therapeutic effect as well as reducing the need for surgical intervention.

Conclusion

Pre-ovulatory saline hydrotubation is a simple cost effective method that increases significantly pregnancy rates in infertile couples treated by ovarian hyper-stimulation with IUI with negligible or no side effects or contraindications.

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