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Physical Endometrial Handling after Failed IVF and Cycle Outcome

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Abstract

Background: Negotiation between the embryo and endometrium in addition to endometrial receptivity is mainly hpothesized as the two main molecular and cellular factors involved in the process of implantation.

Aim: To study and explore the effect of local endometrial scratching, hydrotubation and saline infusion on IVF outcome after failed one past IVF trial.

Study Design: A prospective, randomized, control trial. Setting: Banoon IVF Center. Patients and methods: A total of 800 women either with unexplained or with mild male factor infertility were divided randomly into four groups.

In hydrotubation group 200 women, endometrial scratching group, 200 women and in saline infusion group, 200women, control group 200 women no intervention has been made. For every study category, folliculometry started at cycle day 7 at oocyte retrieval day endometrial scratching have been made in one study category, saline infusion in another study category, hydrotubation in the third study category and no intervention in the fourth study category.

Results: The live birth rates were statistically significantly greater in the hydrotubation, endometrial scratching and saline infusion study subjects compared to the control group (p-values 0.001, 0.001, 0.036 respectively).

Conclusion: Hydrotubation, Endometrial scratching and intra uterine saline infusion are useful in increasing biochemical, clinical and live birth rates after failed previous IVF trials.

Introduction

Unexplained infertility is a clinically diagnosed scenario when there are no obvious or clear etiologies for infertility based on regular infertility assessment parameters and tools [1]. Failure of implantation is a possible etiology for unexplained infertility [2]. Implantation is the corner stone rate limiting step in IVF as regard outcome. Implantation is featured at cellular and molecular basis by normal cellular adhesion or fixation of good quality embryo to a physiologically receptive endometrial lining within a critical time period which is known as and defined by authors as the window of implantation [3]. During this window of implantation, there is perfect cellular and molecular communication and negotiation between the embryo and the endometrial lining.

Many and variable molecules and receptors are have a critical and a corner stone influence in cellular signaling and having a crucial role in the embryo implantation coursed sequence of events, involving cytokines, growth factors and interleukins which are secreted and synthesized by the endometrial lining playing a similar role as an endocrine organ, in addition to altering and adjusting the degree of endometrial receptivity, disruption of these factors, can cause failure of implantation process [4-6].

Evidence obtained from different and variable research studies support that endometrial physical injury and handling in IVF cycles directly after oocyte retrieval will not cause any harm on the embryo implantation cellular and molecular process [5,6].

SIS is an approach by which an IUI catheter is inserted into the endometrial cavity, and sterile saline is injected to split the walls of the endometrium [7]. Saline infusion sonography has proven to be an efficient and precise method in uterine cavity assessment with great margin of safety [8].

Enhancing and augmenting of implantation, by endometrial physical handling has occupied many fertility researchers and has promptly became integrated into clinical performance of fertility

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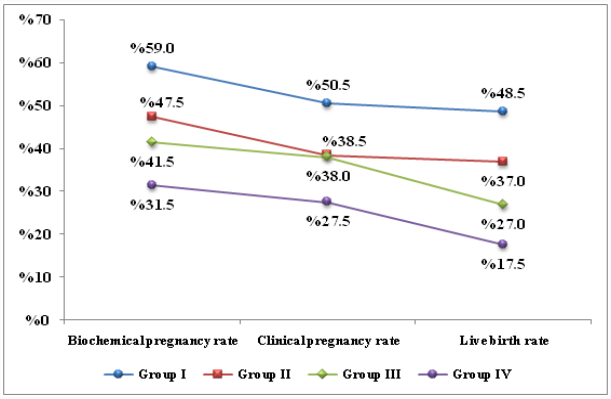

Figure 1: Diagram illustrating Biochemical, Clinical pregnancy and Live birth rate in the four groups.

centers. It has been displayed that physical handling of the endometrial lining can enhance and augment receptivity by tuning gene expression of molecular factors required for successful implantatione. glaminin alpha 4, integrin alpha 6, matrix metalloproteinase 1,5 and glycodelin A. 6A rapid regenerative course at cellular and molecular level after endometrial injury could slow down the unbalanced endometrial maturity which is often accompanied with ovarian stimulation cycles therefore, retuning embryonic endometrial dialogue assisting implantation [9]. Another potentially vital mechanism by which endometrial injury may raise endometrial receptivity is through local increased synthesis and secretion of growth factors and pro inflammatory cytokines [10,11].

The aim of the study was to assess the effect of local endometrial physical manipulation using endometrial scratching *vs.* intrauterine saline infusion on incidence of clinical pregnancy rate after failed one IVF trial.

Patients and Methods

This is a prospective, randomized, control trial constructed to evaluate the impact of hydrotubation *vs.* endometrial scratching *vs.* intrauterine saline infusion *vs.* no intervention on enhancing clinical pregnancy rates in IVF trials. Patients recruited to be involved in this study gave their written informed consent before beginning. After approval of the local ethics committee, the study was conducted between March 2015 and December 2017 at Banoon IVF Center, Egypt.

Patient recruitment and treatment

This study was performed on referred women either those with unexplained or those with mild male factor infertility and after failed previous one IVF cycle trial.

A total of 800 patients were recruited for the study. They had the following **inclusion criteria**: female age 20–35 years with normal basal hormonal profile [FSH, LH] 3–10 mIU/ml and 1.8–8.5 mIU/ml respectively, normal endometrial cavity patency of both tubes as evaluated by HSG, and normal semen analysis. However, mild male factor infertility was defined when there was 2 or more semen analysis with 1 or more items below the 5th centile as defined by the WHO, 2010 [12]. **Exclusion criteria** were patients with unilateral tubal blockage, history of Ovarian Hyper Stimulation Syndrome (OHSS), reduced ovarian response, endometriosis or multiple female factor. Unexplained infertility was diagnosed when there is a confirmed normal tubal patency, normal semen analysis according to WHO criteria, and ovulatory cycles based on folliculometry and mid-luteal serum progesterone levels [13].

All groups were women planning a second full IVF/ICSI cycle with a regular indication for IVF/ICSI and failure of implantation after one full ART cycle. At least one embryo (either fresh or frozen/thaw) must have been transferred during the first IVF/ICSI cycle.

All women underwent GnRH antagonist protocol as follow: controlled ovarian stimulation (COS) started using recombinantFSH (rFSH, Gonal-F; Merck Serono SA, Geneva, Switzerland) 225-400 IU/day for the first five days. Subsequently, the rFSH dose was adjusted along with ovarian response, every other day.

After oocyte retrieval in the same setting or 3 days before embryo transfer patients were according to their group undergone one of the following:

Hydrotubation group: Patients were involved in this group ,the following steps have been performed , with the patient in the

Table 1: Comparison between the four groups.

	Group I	Group II	Group III	Group IV	P value
Age	29.47 ± 3.34	29.62 ± 3.39	29.68 ± 3.51	29.71 ± 3.24	0.888
BMI	27.23 ± 4.45	27.16 ± 4.47	26.75 ± 4.71	27.42 ± 5.18	0.541
Duration of infertility	4.58 ± 1.74	4.55 ± 1.71	4.46 ± 1.31	4.68 ± 1.57	0.587
FSH	5.94 ± 0.84	5.76 ± 0.58	5.77 ± 0.87	5.79 ± 0.86	0.091
LH	5.69 ± 0.73	5.64 ± 0.58	5.63 ± 0.74	5.62 ± 0.95	0.815
Days of stimulation/day	11.94 ± 1.34	11.76 ± 1.33	11.69 ± 1.77	11.59 ± 1.78	0.15
Total number of follicles	7.13 ± 1.46	7.06 ± 1.7	7.02 ± 1.7	7.02 ± 1.71	0.915
Mean follicles diameter (mm)	21.18 ± 0.81	21.14 ± 0.8	21.13 ± 0.71	21.07 ± 0.69	0.545
Endometrial thickness/mm	11.26 ± 1.2	11.17 ± 1.93	11.16 ± 1.59	11.12 ± 1.62	0.848
Biochemical pregnancy rate	118 (59)	95 (47.5)	83 (41.5)	63 (31.5)	<0.001
Clinical pregnancy rate	101 (50.5)	77 (38.5)	76 (38)	55 (27.5)	<0.001
Live birth rate	97 (48.5)	74 (37)	54 (27)	35 (17.5)	<0.001

Group I = IVF Hydrotubation
Group II = IVF Saline infusion
Group III = IVF Endometrial scratching
Group IV = IVF Control

Table 2: Pairwise comparisons between the four groups.

	I*II	I*III	I*IV	II*III	II*IV	III*IV
Age	0.971	0.915	0.888	0.997	0.992	1
BMI	0.999	0.741	0.977	0.821	0.945	0.485
Duration of infertility	0.997	0.867	0.932	0.943	0.849	0.517
FSH	0.124	0.144	0.254	1	0.984	0.992
LH	0.904	0.875	0.812	1	0.997	0.999
Days of stimulation/day	0.631	0.378	0.114	0.977	0.723	0.92
Total number of follicles	0.979	0.929	0.919	0.997	0.995	1
Mean follicles diameter (mm)	0.943	0.918	0.469	1	0.812	0.851
Endometrial thickness/mm	0.951	0.926	0.82	1	0.987	0.994
Biochemical pregnancy rate	0.021	<0.001	<0.001	0.227	0.001	0.038
Clinical pregnancy rate	0.016	0.012	<0.001	0.918	0.019	0.025
Live birth rate	0.02	<0.001	<0.001	0.032	<0.001	0.022

Table 3: Univariate analysis for live birth.

	Live birth		
	+VE (n=260)	-VE (n=540)	P value
Age	29.64 ± 3.41	29.61 ± 3.35	0.9
BMI	26.96 ± 4.57	27.23 ± 4.77	0.45
Duration of infertility	4.53 ± 1.62	4.59 ± 1.58	0.618
FSH	5.93 ± 0.78	5.76 ± 0.8	0.004
LH	5.74 ± 0.71	5.6 ± 0.78	0.011
Days of stimulation/day	11.72 ± 1.5	11.76 ± 1.61	0.733
Total number of follicles	7.13 ± 1.65	7.02 ± 1.64	0.357
Mean follicles diameter (mm)	21.19 ± 0.78	21.1 ± 0.74	0.091
Endometrial thickness/mm	11.55 ± 1.35	11 ± 1.69	<0.001

lithotomy position, and a Cusco speculum positioned in the vagina and the cervix is satisfactorily exposed and gently cleaned by a moist swab with saline. A re-sterilized softWallace catheter (Smiths Medical, London, UK) is inserted in the cervix to pass across the internal os; if resistance or difficulty occurs, a re-sterilized firm Cook catheter (Cook Medical Brisbane, Australia) is introduced, 50 ml of saline is injected slowly but continuously in the uterine cavity. After the injection, the patient is instructed to rest for 10 min and is directed to

come on the next day for embryo transfer Leakaging of saline when performing hydrotubation is expected with variable amounts in all patients. Anyway, as the total volume of injected saline was huge (50 ml), the leaked saline was only a fraction of the volume injected.

Endometrial scratching group: Endometrial scratching using embryo mucus aspiration catheter (Rocket medical) which is a small, flexible catheter used to scratch the endometrial cavity tenderly after cutting the tip of the catheter sheath obliquely.

The procedure of the endometrial scratch was performed as follows:

1. Patient in Lithotomy position.

2. Speculum inserted into the vagina for cervical exposure which is cleaned with sterile gauze.

3.The sheath is inserted into the uterus through the cervical canal after cutting its edge obliquely.

4. Once the sheath is in place, the plugger is removed.

5. The lining of the posterior and anterior wall of the uterus is lightly scratched by inserting and moving the sheath catheter up and down under visualization by transvaginal ultrasound.

The saline infusion group: After sterilization with Povidone iodine (10%) and full irrigation with normal saline, intrauterine insemination (IUI) catheter (Biorade, Berkeley, California) was introduced gently into the uterine cavity with a syringe and then 20 ml of normal saline was introduced into the uterine cavity and aspirated immediately.

The control group: None of previous interventions were made.

A biochemical pregnancy was defined by a finding of plasma b-hCG concentration>10 mU/ml two weeks after embryo transfer. A clinical pregnancy was defined as visualisation of an intrauterine gestational sac with a heartbeat 3 weeks after a positive pregnancy test.

Statistically analysis

Data were revised, entered and analyzed by using SPSS (Statistical Product and Service Solutions) version 19. Pairwise comparisons between the four groups have been performed, univariate and multi variate analysis of live birth have been calculated, P<0.05 was considered statistically significant.

Results

This prospective randomized controlled study was performed to evaluate the effects of local endometrial scratching, hydrotubation, intra uterine saline infusion on fertility outcome which was done before the step of embryo transfer of the same cycle after one failed previous IVF trial.

The observation showed that when comparing four groups together regarding demographic data, hormonal profile and IVF outcome there was no statistically significant difference in age, BMI, duration of infertility, FSH, LH, days of stimulation, total number of follicles, mean follicular diameter, endometrial thickness, however statistically significant difference existed regarding Biochemical, Clinical, and live birth rates showing p a value <0.001.

Analysis and interpretation of the results using pair wise comparisons between four groups have shown the following;

Table 4: Multivariate analysis (predictors) of live birth.

	P value	OR	95% CI
Age	0.587	0.988	0.944 - 1.033
BMI	0.188	0.978	0.946 - 1.011
Duration of infertility	0.342	0.954	0.865 - 1.052
FSH	0.213	1.144	0.926 - 1.414
LH	0.156	1.174	0.941 - 1.465
Days of stimulation/day	0.091	0.919	0.833 - 1.014
Total number of follicles	0.639	1.023	0.93 - 1.125
Mean follicles diameter (mm)	0.006	0.852	0.76 - 0.955
Endometrial thickness/mm	<0.001	1.214	1.1 - 1.34
Group I	<0.001	4.415	2.77 - 7.036
Group II	<0.001	2.749	1.717 - 4.403
Group III	0.036	1.683	1.035 - 2.735

Statistically significant differences existed when comparing;

-Group 1 and 2 as regard biochemical, clinical, and live birth rate with p values 0.021, 0.016, 0.020 respectively showing better IVF outcome in hydrotubation group in comparison with saline infusion group.

-Group 1 and 3 as regard biochemical, clinical, and live birth rate with p values <0.001, 0.012, <0.001 respectively revealing favored IVF outcome in hydrotubation group in comparison with endometrial scratching group.

-Group 1 and 4 as regard biochemical, clinical, and live birth rate with p values <0.001 in all 3 categories showing better IVF outcome in hydrotubation group in comparison with control group.

-While group 2 and 3 showed only statistically significant difference in live birth rate having p value=0.032. Suggesting and implying better live birthrate in saline infusion group than endometrial scratching group.

-Additionally comparing group 2 and 4 showed statistically significant difference in biochemical ,clinical and live birth rate with p values 0.001, 0.019, <0.001 respectively leading to result that reveals better IVF out come in saline infusion group in comparison with control group.

-Lastly comparing group 3 and 4 showed statistically significant difference as regard biochemical, clinical and live birth rate with p values 0.038, 0.025, 0.022 respectively showing better IVF out come in endometrial scratch group in comparison to control group.

Univariate analysis for live birth rate have shown statistically difference in live birth rate as regard FSH, LH, and endometrial thickness showing p value 0.004, 0.011, <0.001 respectively.

Multivariate analysis (predictors) of live birth rate have shown statistical significance as regard mean follicular diameter, endometrial thickness, group 1,2,3 showing p values 0.006, <0.001, <0.001 <0.001, 0.036 respectively.

Discussion

These data are consistent with results outcome from a study performed by Abdelhamid [7], he compared the cycles results after endometrial scratching in the cycle preceding IUI versus scratching in the procedure cycle comparing both to the traditional IUI. He revealed that performing the endometrial mechanical manipulation in the form of scratching significantly enhances pregnancy rates when it is done in the proliferative phase of the IUI cycle, or the cycle preceding IUI, than pregnancy rates with IUI alone 36% *vs.* 38% *vs.* 18%, respectively. Possible explanation of these similarities between their and our results may be attributed to endometrial decidualization caused by either scratching or injury making the endometrial lining more receptive and increase successful implantation. Another group of researchers performed a similar study which was performed out by Zhou et al. [14] they also studied and assessed the impact of local endometrial physical manipulation on IVF cycle and incidence of embryo implantation. They came to a conclusion that localized injury procedure to the endometrium was beneficial for the process of implantation, clinical pregnancy, and live birth rates.

Interestingly in addition both a systematic review and meta-analysis were performed by El Toukhy et al. [15,16], and uncovered the fact that localized injury to the endometrial before performing IVF cycle could lead to elevated opportunities of implantation and successful pregnancy rates.

Another group of researchers explained the mechanism of action at molecular level and cellular level [17], discovering that endometrial biopsy-induced inflammatory mechanism may smooth the progress of preparing the endometrium lining for successful implantation by raising interleukin-15 (IL-15), tumor necrosis factor TNF-a and macrophage inflammatory protein 1 B (MIP-1B) expression.

Contradictory to our findings Baum et al found in a study performed by his research group that endometrial injury by Pipple twice in follicular and luteal phase before IVF cycle didn't show any beneficial effect in patients with recurrent implantation failure patients and clinical outcomes in the study group were statistically significantly lower than those in the control group [14].

Conclusion

Endometrial physical manipulation either by Hydrotubation and saline infusion, intra uterine or endometrial scratching 3 days before embryo transfer is valuable in raising biochemical , clinical pregnancy and live birth rates in women after failed single trial IVF.

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