

Effect of Endometrial Cavity Fluid on Pregnancy Rate of Fresh Versus Frozen *In Vitro* Fertilization Cycle

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ABSTRACT

Objective: This study aims to study the difference in etiology and outcome in terms of implantation rate and abortion rate in fresh (self-stimulated) versus frozen (oocyte donation cycle) *in vitro* fertilization (IVF) and in transient versus persistent fluid. **Material and Methods:** This retrospective study was conducted in the Department of Reproductive Medicine of tertiary care center from January 2012 to November 2015. Data were collected retrospectively from the departmental files. Twenty-four patients from fresh IVF-stimulated cycles and 24 from frozen oocyte donation cycle with their endometrium prepared by hormone replacement treatment were included in the study. All patients selected in the study had grade-A embryo transfer of day 3–4 with maximum three embryo transferred. Pregnancy was defined by rising serum beta-human chorionic gonadotrophin levels performed after 14 days of embryo transfer and further confirmed by ultrasonographic visualization of gestational sac at 6 weeks. All biochemical pregnancies were included in implantation failure. All pregnant patients were followed till the termination of pregnancy and further noted as live birth or abortion. **Results:** Clinical pregnancy rate was seen more in self-stimulated cycle (62.5%) with live birth rate of 50% than hormone replacement treatment cycle, in which clinical pregnancy rate was 45.83% with live birth rate of 33.33%. Clinical pregnancy rate was highest in group with very less fluid in cavity (1–2 mm) 63% and with live birth of 52.63%. Clinical pregnancy was seen only in two patients of group B with anterior and posterior (AP) diameter of fluid in cavity of 2–3 mm with live birth of only one, whereas in group C, with AP diameter of 3–5 mm, none of the patient conceived. This difference was statistically significant. Clinical pregnancy rate was 65.62% in transient fluid accumulation with live birth rate of 53.25%, which was significantly higher than persistent fluid accumulation (P value – 0.0337 for pregnancy rate and 0.0312 for live birth rate). **Conclusion:** Fluid accumulation seen in fresh cycles are generally associated with better outcome because it may be associated with good prognostic factors – small AP diameter of fluid, with transient fluid accumulation and more with poly cystic ovarian syndrome as an etiological factor; however, in frozen cycle, it can be associated with poor outcome.

KEYWORDS: Endometrial cavity, frozen IVF cycle, pregnancy, self-stimulated *in vitro* fertilization

INTRODUCTION

Infertility is a common problem affecting about 15% of population in reproductive age group. Of these, 40–50% are due to female causes of infertility.^[1] In the last few years, assisted reproductive technology (ART) has taken big leaps forward, and as possibly leading

to many more couples being offered IVF treatment, although the increasing numbers of ART centers in both

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the developed and developing countries may also be a contributing factor. The point of lower costs of treatment is now a days has also contributed dramatically to the increasing numbers of IVF treatment and an up liftment in the general economic status of the middle class making treatment feasible and within reach.^[2]

Even though lots of research is being conducted in different parts of the world in the field of IVF, but the success rates of IVF/ICSI cycle are still low. Of all couples who undergo IVF/ICSI cycle, the live birth rate is of the order of only 30% per oocyte retrieval.^[3] The disturbance between the embryo and maternal signaling is considered as the major (60%) cause of termination of the pregnancies at the end of the peri-implantation period.^[4] Many factors have been studied for the causative reason of implantation failure. The presence of fluid in endometrial cavity is possibly an important cause of implantation failure. Patho-physiology of endometrial fluid remains unclear. However, it was found to be associated with hydrosalpinges, polycystic ovarian disease, sub clinical uterine infections, and generated physiologically by the genital tract. It is also seen transiently during ovarian stimulation and after receiving a HCG injection in an IVF cycle.^[5]

Many studies have revealed IVF cycles with presence of fluid in cavity generally have a low implantation and pregnancy rate, and high incidence of cancelation of cycles, especially when associated with hydrosalpinges.^[6-9] Previous studies have found that tubal factor of infertility even in the absence of hydrosalpinx, is the main cause of accumulation of fluid within the uterine cavity during the IVF treatment.^[7] Relatively very few studies have been conducted on fluid in endometrial cavity, and all these have focused upon the fresh cycle transfer. Whether there is any difference in etiology and pregnancy outcome in fresh versus frozen cycle with fluid in endometrial cavity or not?, This question still remains unanswered.

Therefore, present study was conducted to study the difference in etiology and outcome in terms of implantation rate and abortion rate in fresh versus frozen IVF cycle and in transient versus persistent fluid.

MATERIAL AND METHODS

This study was conducted in a retrospective manner in the Department of Reproductive Medicine of tertiary care center from January 2012 to November 2015. Data were collected retrospectively from the departmental files. All patients who had fluid in endometrial cavity during the course of ovarian stimulation and endometrial preparation in egg donation cycles were recruited for the study. Further note was made from file, for the presence

of fluid during the previous mock cycle conducted in both fresh and frozen cycle patients. Those patients, in whom fluid was noted during previous mock cycle, were labeled as persistent fluid accumulation, and in those, who did not have fluid, were labeled as transient fluid accumulation. Twenty-four out of 750 patients, from fresh IVF-stimulated cycles and 24 out of 846 patients who underwent frozen oocyte donation cycle with their endometrium prepared by hormone replacement treatment were included in the study. All those patients, in whom fluid was noted during stimulation cycle, and embryo transfer was not performed, were excluded. Patients in whom fluid accumulation was seen following HCG injection at the time of oocyte retrieval were also excluded from the study to reduce bias because we compared our results with frozen cycles, in which HCG was not given and previous studies have shown that fluid accumulation during HCG injection does not affect the IVF cycle outcome.^[10] Patients with uterine pathologies affecting implantation rates like submucosal and intramural fibroid, adenomyosis were excluded.^[11-13] Patients with cervical stenosis were also excluded from the study group.

The cause of fluid in the endometrial cavity was noted from file, and they were divided into four factors: tubal, PCOS, uterine, and unexplained factors. The diagnosis of PCOS was based on the current Rotterdam criteria, which is based on presence of oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries.^[14] The tubal factor patients were identified mainly by hysterosalpingography and laparoscopy. The unexplained factors included all those cases in which cause of fluid could not be ascertained. In uterine factor, cases with endometritis and Asherman's as evidenced by hysteroscopy were included.

Ultrasonographic examinations were performed with a 5 MHz multi-frequency transvaginal probe. Note was made for the presence of fluid accumulation which was defined as an echolucent ring configuration distended by a certain amount of fluid as seen by transvaginal ultrasound. Fluid diameter between the anterior and posterior (AP) endometrial linings in a sagittal view of uterine cavity was noted. In the cases of fluid accumulation, the endometrium thickness was measured by subtracting the maximal fluid diameter from the maximal distance between the opposing myometrial/endometrial interfaces.

All patients selected in the study had grade-A embryo transfer of day 3-4 with maximum three embryos transferred. Pregnancy was defined by rising serum beta-HCG levels performed after 14 days of embryo transfer and further confirmed by ultra sonographic visualization of gestational sac at 6 weeks. All

biochemical pregnancies were included in implantation failure. All pregnant patients were followed till the termination of pregnancy and further noted as live birth or abortion.

RESULTS

A total of 48 patients were included in the study, according to inclusion and exclusion criteria. Twenty-four patients were in the fresh cycle and 24 in frozen cycle. Incidence of fluid in cavity was 3.2% in fresh cycle and 2.8% in frozen cycle. Mean age of all the patients in fresh cycle was 32 years. In frozen cycle, although the age of patients was high, but mean age of donors was same as in self-stimulated cycle. Endometrial thickness in all patients on the day of pick up in fresh cycle and on day of starting progesterone in frozen cycle was similar about 7–9 mm.

Table 1 compared the fresh and frozen cycle patients on the basis of different AP diameter of fluid in cavity and transient versus persistent fluid and its outcome. Number of patients with group A were more in fresh cycle^[15] as compare to frozen cycle.^[16,17] Whereas, three patients of group C with AP diameter of 3–5 mm were seen only in frozen cycle. However, this difference was not statistically significant. In stimulated cycle out of 24 patients, 21 were having transient fluid, and only three were having persistent fluid. Whereas in HRT cycle; 13 patients had persistent fluid, with 11 having transient fluid accumulation. This difference was statistically significant.

Clinical pregnancy rate was seen more in fresh cycle (62.5%) with live birth rate of 50% and in frozen cycle clinical pregnancy rate was 45.83% with live birth rate of 33.33%. Although this difference, was not statistically significant.

Table 2 shows the fluid levels in different AP diameter and its clinical outcome. Maximum number of patients were in group A – 38 (79.16%), in group B – 7 (14.53%), and in group C – 3 (6.2%) patients. Clinical pregnancy rate was also highest in group A–63% and with live birth of 52.63%. Clinical pregnancy was seen only in two patients of group B with live birth of only one, and in group C, no pregnancy was seen. This difference was statistically significant.

Table 3 compares the outcome of transient fluid accumulation with 32 patients versus persistent fluid accumulation with 16 patients. Clinical pregnancy rate was 65.62% in transient fluid accumulation with live birth rate of 53.25%, which is significantly higher than persistent fluid accumulation (*P* value – 0.0337 for pregnancy rate and 0.0312 for live birth rate).

Table 1: Distribution of patients in stimulated and HRT cycle according to AP diameter and on basis of transient versus persistent fluid and its outcome

	Stimulated cycle	HRT cycle	<i>P</i>
AP diameter			
Group A (1-2 mm)	21	17	0.168
Group B (2-3 mm)	3	4	
Group C (3-5 mm)	0	3	
Fluid accumulation			
Transient	21	11	0.005
Persistent	3	13	
Clinical pregnancy rate	15 (62.5)	11 (45.83)	0.3852
Live birth rate	12 (50%)	8 (33.33)	0.3801

Table 2: Distribution of patients according to AP diameter and its outcome

AP diameter	Group A (1-2 mm)	Group B (2-3 mm)	Group C (3-5 mm)	<i>P</i>
No. of patients	38 (79.16)	7 (14.53)	3 (6.2)	
Pregnancy rate (%)	24 (63.15)	2 (28.57)	0	0.0363
Live birth rate (%)	20 (52.63)	1 (14.28)	0	0.049

Table 3: Distribution of patients according to transient versus persistent fluid and its outcome

Type of fluid	Transient	Persistent	<i>P</i>
No. of patients	32	16	
Pregnancy rate (%)	21 (65.62)	5 (31.25)	0.0337
Live birth rate (%)	17 (53.25)	3 (18.75)	0.0312

Table 4 compares different etiological factors for fluid accumulation in uterine cavity in transient versus persistent fluid accumulation and in fresh and in frozen cycle. Out of these tubal factor was the major cause in both transient and persistent fluid accumulation and also in fresh and frozen cycle. PCOS was seen in only five patients with transient fluid accumulation and in fresh IVF cycle only. Uterine factor was seen in five patients in persistent and only two in transient fluid accumulation. Similarly uterine factor was seen in six patients of frozen cycle with one patient in fresh cycle. Unexplained factor was seen in 12 patients with transient fluid with only one patient with persistent fluid. As we compare fresh and HRT cycles, it was seen in seven patients in fresh cycle with five patients in HRT cycle.

DISCUSSION

Although the incidence of fluid accumulation in uterine cavity is less, but its presence is detrimental to embryo implantation.^[6-9] The fluid inside the cavity can adversely affect the cell proliferation or interfere with early stages of embryo implantation such as “apposition” and “attachment.”^[4] Limited studies have been conducted on fluid in cavity. All previous studies were limited to fresh

Table 4: Distribution of etiological factors in patients with transient and persistent fluid and in patients with fresh and HRT cycle

Causes of fluid in cavity	Transient	Persistent	P	Fresh	HRT	P
Tubal	14	8	0.0097	10	12	0.0319
PCO	5	0		5	0	
Uterine	2	5		1	6	
Unexplained	12	1		7	6	

IVF-stimulated cycles with fluid in cavity. Our study has compared the outcome on 48 patients with fluid in cavity with fresh IVF-stimulated cycle compared with frozen cycle.

He *et al.* did study on 46 patients with fluid in endometrial cavity.^[6] They found decrease in clinical pregnancy rate with increase in AP diameter with no clinical pregnancy in patients with AP diameter beyond 3.5 mm. Our study has shown similar results. Clinical pregnancy rate and live birth rate are not affected by very less amount of fluid in cavity (1–2 mm). Because the AP diameter of fluid increases, it affects the outcome of cycle with no clinical pregnancy seen beyond AP diameter of 3 mm. As we compare IVF fresh cycle and frozen cycle, similar pregnancy outcome seen, as AP diameter of fluid increases there is decrease in clinical pregnancy rate and live birth rate and this difference is clinically significant.

Previously many studies have shown that transient fluid accumulation does not adversely affect clinical pregnancy rate and live birth rate,^[6-9] similarly, in our study also, pregnancy rate was significantly higher (65.2%) as compared to persistent fluid (31.25%). As we compare frozen and fresh cycles, persistent fluid was seen more in frozen cycle and was associated with poor outcome.

In our study, we have seen that tubal factor is the major cause of fluid accumulation in endometrial cavity, although seen more in transient fluid accumulation compared to persistent fluid accumulation and. Similar results were seen in previous studies also.^[7] As previously reported in literature, there is a strong association between poor outcome in IVF cycle with hydrosalpinx and its frequent association with fluid accumulation.^[16,18,19] We routinely do laproscopic tubal clipping or salpingectomy with cases diagnosed with hydrosalpinx undergoing IVF cycle. From 22 patients with tubal factor, five were associated with hydrosalpinx, but its outcome could not be explained on the basis of hydrosalpinx because operative intervention was performed earlier.

PCOS as an etiological factor was seen only in transient fluid accumulation and in fresh IVF self cycle. Akman *et al.* had shown that endometrial cavity fluid associated with PCO in IVF cycles has good outcome as compared to

cases with tubal factor.^[8] In our study also, we have seen similar results. Out of five PCO patients, three conceived in their first IVF cycle, whereas out of 22 patients with tubal factor, only 10 patients conceived although sample size is very small to draw any conclusion. Uterine factor was seen more, in persistent than that in the transient fluid accumulation and more in HRT cycle.

Previous literature has also shown better pregnancy outcome in frozen cycle as compared with fresh cycle.^[20,21] In our study population, non-ECF group had similar outcome in both fresh and frozen cycle (clinical pregnancy rate (68.3%) and live birth (56%) rate in frozen cycle and (65% – CPR and LBR – 54.2% in fresh cycle, however in ECF group better pregnancy outcome was seen in fresh cycle in comparison to frozen cycle. It may be reason that fresh cycles with fluid in cavity are associated with good prognostic factors – small AP diameter of fluid, with transient fluid accumulation and more with PCOS as an etiological factor.

CONCLUSION

We can conclude that fluid accumulation seen in self-stimulated cycle is generally associated with better outcome; however, if it is seen in HRT cycle, it can be associated with poor prognosis. One may try to aspirate the fluid with embryo transfer catheter.^[15,22] Transmyometrial transfer may be an alternative method,^[23,24] but its effectiveness is not proven yet.

Limitation of our study is that we have compared the outcome of fresh cycle with frozen oocyte donation cycle, although the mean age of patients undergoing fresh cycle was same as that of donors of oocyte donation cycle. Further large studies are required to draw any conclusion.

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Conflicts of interest

There are no conflicts of interest.

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