First Trimester Pregnancy Loss May Temporary Reduce the Ovarian Response during the Subsequent IVF Cycle

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Abstract

The aim of this study was to compare the *in vitro* fertilization (IVF) cycles ended by miscarriage with subsequent IVF cycles in relation to various IVF cycle parameters and pregnancy termination modalities. Comparison of pre-miscarriage to post-miscarriage IVF cycles parameters demonstrated that lower peak E_2 levels (1087 ± 593 versus 1237 ± 676 pg/ml, respectively; $p < 0.05$) were achieved in the post miscarriage cycles despite higher total gonadotropin consumption (2341 ± 1488 versus 2115 ± 1101 IU; $p < 0.05$). A greater endometrial thickness (10.4 ± 2.16 versus 9.98 ± 1.74 mm, respectively; $p < 0.05$) and a higher number of embryos (4.62 ± 2.63 versus 3.78 ± 2.54, respectively; $p < 0.05$) were observed in the pre-miscarriage cycles. A comparison of IVF parameters between the first and second IVF cycles following miscarriage showed an increase in peak estradiol level (954 ± 800 and 1257 ± 838 pg/ml, respectively; $p < 0.05$), an increased number of retrieved oocytes (7.38 ± 4.2 and 10.49 ± 4.99, respectively; $p < 0.05$), more fertilized embryos (3.87 ± 2.38 and 5.66 ± 3.64, respectively; $p < 0.05$), and an increase in the conception rate (34.7% versus 42.2%, respectively) at the second post-miscarriage IVF cycle.

Keywords

IVF, Miscarriage, First Trimester Pregnancy Loss, Superovulation, Ovarian Response, Endometrial Thickness, Conception Rates

1. Introduction

Approximately 5% of *in vitro* fertilization (IVF) cycles end with an early preg-

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nancy loss, representing 15% of pregnancies occurring after IVF [1]. The true incidence of miscarriage, however, is not well established as many of the pregnancy losses occur before pregnancy can be clinically recognized. After fertility treatment and particularly after IVF treatment, the diagnosis of pregnancy is made at an early stage compared to spontaneous pregnancies. Most women who undergo fertility treatment are highly motivated to have a pregnancy follow up at an early stage of the pregnancy, whereas data from spontaneous pregnancies is difficult to ascertain. There is no solid data to compare the incidence of miscarriage in spontaneous versus IVF pregnancies, but it is generally accepted that the incidence of miscarriage is slightly higher after IVF treatment [2] [3]. Little is known about the significance of prior early pregnancy loss on future IVF cycles. The literature contains conflicting data concerning the prognostic value of an early permanency loss on subsequent IVF cycles, some reported higher success rates after first trimester miscarriage during the next IVF attempt [4] [5]. Younger maternal age, premature rupture of membranes, intra-uterine growth restriction, hypertensive disorders, and preeclampsia are all independently associated with an initial miscarriage [6].

Once a spontaneous pregnancy loss has been diagnosed, there are three forms of management: expectant, medical, or surgical. The optimal mode of management is determined by gestational age, whether the pregnancy loss is delayed or incomplete, maternal hemodynamic stability, infection, and most importantly patient preference. Surgical management involves sharp curettage, vacuum aspiration, or a combination of both [7]. It is used in 80% of the cases, and considered the most common procedure used to manage spontaneous miscarriages. There is controversy about the complications after a surgical management. While some say that surgical management increases the risk of obstetrical complications and adverse perinatal outcomes [6], other studies show no evidence of such [8]. Medical management is an excellent alternative for women desiring minimal intervention. Such management is successful in 66% to 99% of women with incomplete or delayed pregnancy loss in the first trimester. Medical treatment typically begins with misoprostol, a prostaglandin E1 analog, whereas some regimens include mifepristone (a progesterone receptor antagonist) in combination with misoprostol [7]. Although little is known about the post-medical miscarriage complications, there are still controversies in different studies. Some studies show an increase of ectopic pregnancies [9], while others show no difference between medical and surgical termination of pregnancy [8] [9].

The objective of the present study was to address the widespread discrepancy of outcomes of IVF cycles after miscarriages and to investigate the impact of medical, surgical, and expectant miscarriage management after IVF on the subsequent IVF treatment outcome.

2. Methods and Patients

The present retrospective cohort study included data from 138 women who had a first trimester pregnancy loss following IVF. In this particular patient popula-

tion, 417 IVF cycles prior to and post-miscarriage that occurred between the years 2004 and 2016 have been analyzed. The data was retrieved from patient charts at Soroka University Medical Center, analyzed, compared, and included in the study. The study was approved by the local Institutional Ethics Committee.

Cycles that ended with chemical miscarriages, late miscarriages, ectopic pregnancies, and patients with recurrent pregnancy loss were excluded from the study.

The miscarried 138 IVF cycles were categorized by the mode with which the pregnancies were managed: 81—surgically terminated (sharp curettage), 13—medically terminated, and 44 pregnancies—managed expectantly without intervention. The following patient characteristics have been retrieved and compared: patient age, spouse's age, basic hormonal levels, smoking, BMI.

The 417 IVF cycles, namely 181 prior to and 236 IVF cycles subsequent to the miscarriage have been analyzed according to the mode by which the miscarriage was approached. The group of surgical curettage (n = 250) was subdivided into 103 prior and 147 post-curettage IVF cycles. The medically managed group (n = 36) was subdivided into 17 prior and 19 post-miscarriage IVF cycles, and expectantly managed category (n = 131) cycles subdivided into 61 prior and 70 post-miscarriage IVF cycles.

The following IVF cycle parameters have been compared between the pre-miscarriage and post-miscarriage cycles: endometrial thickness, peak estradiol (E_2) levels, total gonadotropin consumption per cycle, number of oocytes retrieved, number of fertilized eggs, number of cleavage embryos. Ovarian response was further assessed using the ovarian sensitivity index (OSI) [10]. OSI is the ratio between aspirated oocytes and total dose of FSH used in the cycle.

3. Data Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (version 21, SPSS Inc.). All tests were two tailed, and statistical significance was set at $p < 0.05$. Continuous variables are presented as means and were tested by independent t-test or One-Way ANOVA. Categorical variables comparison was performed by Chi-square test. Multivariate logistic regression was used to characterize the IVF cycle characteristics pre- and post-miscarriage while neutralizing confounding factors such as maternal age, paternal age, ethnicity, smoking, and BMI.

4. Results

Comparing patient criteria including maternal age, paternal age, BMI, smoking, and levels of FSH, LH, and TSH did not demonstrate any statistically significant differences between those who have been managed surgically, medically, or expectantly (Table 1).

Table 1. Patient characteristics according to the mode of pregnancy termination.

Mean ± SD	Total Patients N = 138	Surgical N = 81	Medical N = 13	Expectant N = 44	*p* value
Maternal age (y)	31.52 ± 5.26	32.19 ± 5.39	32.35 ± 5.84	30.06 ± 4.67	0.162
Paternal age (y)	35.17 ± 7.23	35.87 ± 7.80	35.58 ± 8.14	33.83 ± 5.73	0.361
BMI	26.16 ± 6.58	26.22 ± 6.27	27.11 ± 8.76	25.77 ± 6.35	0.581
FSH (IU)	6.85 ± 2.21	6.86 ± 2.32	7.59 ± 2.70	6.64 ± 1.85	0.563
LH (IU)	6.37 ± 5.85	7.39 ± 7.31	5.25 ± 2.50	4.91 ± 2.30	0.127
TSH (mIU)	2.47 ± 1.27	2.67 ± 1.38	2.55 ± 1.58	2.07 ± .80	0.076

Gestational age at the time of pregnancy termination in the abortion pregnancy significantly differed between the various pregnancy termination modes *i.e.* surgical, medical and complete abortions (10.38 ± 4.37, 7.85 ± 1.36, and 6.85 ± 3.95 respectively, $p < 0.01$). IVF protocols and the type of gonadotropins used were comparable between study groups. Analyzing all IVF cycles included in the study (Table 2) regardless of the mode of pregnancy termination, showed that mean endometrial thickness among the 181 IVF cycles prior to the miscarriage was significantly higher compared with the 236 IVF cycles that followed the miscarriage (10.47 ± 2.16 and 9.98 ± 1.74 mm, respectively; $p = 0.003$). Furthermore, the peak estradiol level was found to be higher in the pre-miscarriage compared with post-miscarriage cycles (1237.20 ± 676.29 and 1087.71 ± 593.26 pg/ml, respectively; $p < 0.05$) despite a lower gonadotropin consumption per cycle for the pre-miscarriage cycle (2115 ± 1107 and 2341 ± 1488 IU, respectively; $p < 0.05$). Although the number of oocytes retrieved was similar, the number of embryos available for transfer was higher in cycles prior to the miscarriage compared with the post-miscarriage cycles (4.62 ± 2.63 and 3.78 ± 2.54, respectively; $p < 0.05$). Comparing the OSI in the pre- and post-miscarriage cycles, a non-significant increased OSI was noted in the post miscarriage cycle (4.413 ± 3.49 vs. 4.741 ± 3.64 respectively, $p = 0.509$). However, comparing the post miscarriage cycle to the subsequent one, a significant OSI increase was noted (4.058 ± 3.04 vs. 5.982 ± 5.04 respectively, $p = 0.012$).

Interestingly, analyzing the IVF cycles according to the mode of pregnancy termination has shown the endometrial thickness to not be significantly affected by medical or expectant management of the miscarriages. Surgical termination of pregnancies disclosed a statistically significant reduction of endometrial thickness comparing the pre-miscarriage and the post-miscarriage cycles data (10.79 ± 2.13 and 10.13 ± 1.68 mm, respectively; $p < 0.05$). Although the mean total gonadotropin consumption per cycle was found to be lower in the pre-miscarriage IVF cycles, the number of embryos available for transfer was higher in the pre-miscarriage cycles compared with the post-miscarriage cycles, even though the data did not reach statistical significance (Table 2).

Using multiple logistic regression analysis, controlling for women's age and confounders related to the post-miscarriage IVF cycles, such as peak estradiol

Table 2. Comparison of IVF cycle parameters between cycles prior to and following first trimester pregnancy loss related to the mode of pregnancy termination.

Miscarriage management	IVF cycles	Endometrial thickness (mm)	Peak E$_2$ (pg\ml)	Total gonadotropins per cycle (IU)	Number of oocytes	Number of fertilized oocytes	Number of embryos
Total IVF cycles **n = 417**	Pre-miscarriage n = 181	10.47 ± 2.16	1237 ± 676	2115 ± 1101	9.2±4.7	5.39±2.97	4.62 ± 2.63
	Post-miscarriage n = 236	9.98 ± 1.74	1087 ± 593	2341 ± 1488	9.08 ± 5.61	5.19 ± 3.78	3.78 ± 2.54
	p	0.003	0.041	0.026	0.808	0.583	0.006
Surgical **n = 250**	Pre-miscarriage n = 103	10.79 ± 2.13	1229 ± 694	2183 ± 1056	8.7 ± 4.58	5.07 ± 2.97	4.6 ± 2.65
	Post-miscarriage n = 147	10.13 ± 1.68	1168 ± 580	2458 ± 1675	9.36 ± 6.3	5.3 ± 4.32	4.06 ± 2.92
	p	0.001	0.868	0.052	0.238	0.517	0.224
Medical **n = 36**	Pre-miscarriage n = 17	9.67 ± 1.78	1306 ± 366	1364 ± 781	10.78 ± 5.45	5.35 ± 2.07	4.61 ± 1.83
	Post-miscarriage n = 19	9.41 ± 1.65	657 ± 375	1883 ± 1078	7.71 ± 3.9	5.42 ± 3.15	2.88 ± 1.48
	p	0.741	0.004	0.063	0.064	0.776	0.054
Expect **n = 131**	Pre-miscarriage n = 61	10.25 ± 2.12	1029 ± 724	2139 ± 1218	9.9 ± 4.77	6.06 ± 3.1	4.53 ± 2.69
	Post-miscarriage n = 70	10.0 ± 1.67	1026 ± 584	2194 ± 1091	8.8 ± 4.31	4.91 ± 2.6	3.59 ± 1.95
	p	0.435	0.049	0.557	0.113	0.016	0.052

(E$_2$) level, total gonadotropin consumption, number of oocytes retrieved, and number of embryos obtained, only peak E$_2$ level was significantly associated with a reduced clinical pregnancy rate in post-miscarriage IVF cycles (OR 1.001, CI 1.000 - 1.001, *p* = 0.007).

Comparison of IVF parameters between the first (n = 138) and second (n = 90) cycles following the miscarriage has shown (Table 3) comparable endometrial thickness between the first and the second post-miscarriage cycles with a significantly increasing peak E$_2$ level (954 ± 800.39 and 1257 ± 838 pg/ml, respectively; *p* < 0.05), more retrieved oocytes (7.38 ± 4.2 and 10.49 ± 4.99, respectively; *p* < 0.05), and more fertilized oocytes (3.53 ± 2.74 and 4.28 ± 3.11, respectively; *p* < 0.05), despite a comparable total amount of injected gonadotropins, emphasizing an improved response of the ovaries to gonadotropin treatment. Most importantly, an increased conception rate was obtained among the patients undergoing the second IVF cycle following miscarriage compared with the first post-miscarriage cycle (42.2% versus 34.7%, respectively). The time frame to the first post-miscarriage IVF was 44 - 577 days (mean 202.2) and the time frame to the second IVF was 162 - 590 days (mean 424.7).

5. Discussion

Spontaneous miscarriage refers to a pregnancy that ends spontaneously before

Table 3. Comparison of IVF parameters between the first and the second IVF cycles following pregnancy loss.

IVF cycles following miscarriage	Mean Interval from miscarriage to conception (range in days)	Endometrial thickness (mm)	Peak E$_2$ (pg/ml)	Total gonadotropins per cycle (IU)	Number of oocytes	OSI	Number of fertilized oocytes	Number of embryos	Pregnancies
First cycle n = 138	202.2 (44 - 577)	9.93 ± 1.96	954 ± 800	2396 ± 1252	7.38 ± 4.2	4.058 ± 3.04	3.87 ± 2.38	3.53 ± 2.74	48 (34.7%)
Second cycle n = 90	424.7 (162 - 590)	10.05 ± 2.05	1257 ± 838	2415 ± 1369	10.49 ± 4.99	5.982 ± 5.04	5.66 ± 3.64	4.28 ± 3.11	38 (42.2%)
p		0.552	0.623	0.898	0.001	<0.001	0.013	0.088	0.386

the fetus has reached a viable gestational age. In the majority of cases, single, sporadic, and spontaneous miscarriages have traditionally been attributed to chromosomal abnormalities. However, if chromosomal abnormalities are not the miscarriage cause, other multi-factorial etiologies may be the miscarriage underlying cause. Women with an initial miscarriage have an increased risk for obstetrical complications and adverse perinatal outcomes compared with women with a previous delivery beyond 22 weeks' gestation [7] [11]. The consequences of the miscarriage may impact the subsequent IVF cycle. That was the basis for the current study, addressing these possible impacts such as ovarian response and endometrial thickness among others.

Surprisingly, we have discovered a significantly reduced peak estradiol levels as well as a reduced number of embryos available for transfer, in spite of an increased consumption of total gonadotropins per cycle in the post-miscarriage compared with the pre-miscarriage IVF cycles. Based on our observation, the reduced ovarian response seems to be temporary and still partially present 6 months post-miscarriage with a full recovery observed about 14 months post-miscarriage. The parameters of the ovarian response, such as peak estradiol level, number of oocytes retrieved, OSI and number of fertilized embryos, were significantly increased in the second post-miscarriage cycle compared with the first cycle. In fact, the pregnancy rates were found to be higher among patients having the second post-miscarriage IVF cycle compared with the first post-miscarriage IVF.

It is accepted that a thickening of the endometrium is critical to a successful implantation of embryos in the uterine cavity. There is controversy regarding the clinical significance in variations of endometrial thickness observed among patients undergoing IVF and the association of the endometrial thickness with the conception rates after IVF and ET. It is widely accepted that an adequate thickness of endometrium is indispensable for a successful pregnancy in ART cycles [12]. It is generally accepted that pregnancy does not occur when the endometrium measures <7 mm. Embryo implantation and clinical and ongoing pregnancy rates are significantly higher in patients with an endometrial thickness ≥ 9 - 10 mm [13]. It was observed that when the endometrial thickness is 14 mm and more, the pregnancy rates were significantly lower, and also suggests a

possible increase in spontaneous miscarriage rate [12] [14]. Endometrial thickness is measured in the mid-sagittal plane during transvaginal ultrasound, which is considered both non-traumatic and simple [15].

Many authors suggest a positive relationship between endometrial thickness and pregnancy rates in either autologous or donor oocytes [16] [17] [18] [19]. Significantly higher conception rates have been observed with thicker endometrium in autologous or donor oocytes after IVF cycles [20] [21] [22] [23].

One of the strategies to distinguish between ovarian and uterine factors is to evaluate the results among patients using donated oocytes. Studies have found endometrial thickness to be predictive of the pregnancy rates in patients treated with donor oocytes [22]. Such studies provide further support for the conclusion that endometrial thickness is indicative of endometrial receptivity.

Although our study has shown a statistically significant reduction of endometrial thickness following a miscarriage, particularly one involving surgical treatment, it seems clinically insignificant. Nevertheless, some studies suggest that the magnitude of endometrial thickness may be associated with the reduction of pregnancy rates [24] [25]. Authors such as Moon *et al.* [26] demonstrated the same results as ours regarding endometrial thickness post-dilatation and curettage with recovery of endometrial thickness 6 months post-miscarriage. There were more studies that indicated recovery over different periods of time [19] [20] [21]. An unsolved question is the mechanism of action for the endometrial thickness reduction. Given the reduced ovarian response resulting in lower estrogen levels, one might have thought that the lower estrogen levels reduce the endometrial thickness as estrogen is the hormone that causes the endometrial proliferation. However, as observed in thawed embryo transfers especially in natural cycles, even low levels of estrogen, much lower than estrogen levels in fresh cycles, produces good endometrial thickness and favored cycle outcomes. A possible mechanism is the mechanical impact of a surgical pregnancy termination. This pregnancy termination method did exhibit poorer endometrial thickness in the current study but further studies are still required to establish that association.

In addition, and based on our results, it cannot be excluded that more factors, besides endometrial thickness reduction, can play a role in reduced conception rates post-miscarriage. Therefore, we may speculate that the observed temporary reduction of the ovarian response to gonadotropin treatment and a reduced conception rate in the first IVF cycle following the miscarriage, and the improvement observed at the second IVF cycle following the miscarriage, regardless of a comparable endometrial thickness between the first and the second cycles, demonstrate a recovery of the ovarian response to gonadotropins.

The impact of a miscarriage on a subsequent IVF cycle has been previously studied with contradicting results. While some studies reported a pregnancy loss in IVF cycle as a prognostic factor for future pregnancies, others found that a pregnancy loss does not negatively affect the outcome of the subsequent cycle

and even one suggested it to be a positive predictor [4]. The current study, did reveal an unreported impact on the subsequent cycles in the form of a temporarily reduced ovarian response along with an endometrial thickness reduction. The mechanism of action by which a pregnancy loss reduced the ovarian response is unclear. A possible mechanism may be an interrupted ovarian blood flow. It is well established that ovarian surgical interventions diminish the ovarian reserve and directly impacts subsequent ovarian response. The increased blood flow to the reproductive system via the uterine and possibly the ovarian artery was previously established. It may be estimated that a pregnancy loss deteriorates the increased blood flow maybe as a protective effect thus naturally reducing pregnancy rates via reduced ovarian response. This hypothesis should be further investigated.

The current study has some limitations. First and foremost is its retrospective design. Second, is the lack of information regarding the age of the transferred embryos. We have attempted to overcome these limitations using comprehensive data collection extracted from the Soroka IVF unit records, which were conducted by expert physicians. Also, being the sole medical center in the region in which all women undergoes the IVF cycle as well as the pregnancy surveillance and delivery, also strengthen the study.

Therefore, miscarriage may have a negative effect on endometrial thickness and on the ovarian response to gonadotropins and consequently the subsequent conception rates. We could not find such an observation published in the literature in support of or in contrast to our findings. Moreover, our study was able to distinguish between the detrimental effects of surgically managed miscarriage compared to a medical or spontaneous resolution of the miscarriage. The surgical approach to termination of a pregnancy was clearly related to a reduced endometrial thickness while the medical or spontaneous resolution had no impact on endometrial thickness.

6. Comment

We may conclude that medical termination or expectant management of an early pregnancy loss should be the preferred methods with the purpose to safeguard the endometrial ability to implant embryos in the near future. Miscarriage, regardless of the mode of pregnancy termination, will negatively affect the ovarian response to gonadotropin stimulation and the conception rate in the short term. Therefore, following miscarriage, the subsequent IVF cycle should be postponed at least 5 - 6 months with the purpose to regain endometrial receptivity and normalize the ovarian response to gonadotropins. More and large studies aimed to analyze the ovarian response in addition to endometrial thickness after early pregnancy loss are needed to corroborate our findings.

Conflict

There is no conflict of interest to be reported.

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