ORIGINAL ARTICLE: EARLY PREGNANCY

First trimester pregnancy loss after fresh and frozen in vitro fertilization cycles

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Objective: To characterize risks for early pregnancy loss after fresh and frozen IVF cycles and to investigate whether risk is modified by infertility diagnoses or transfer of embryos in fresh versus frozen cycles.
Design: Retrospective cohort study using data from the National Assisted Reproductive Technology (ART) Surveillance System.
Setting: Fertility centers.
Patient(s): Clinical pregnancies achieved with fresh and frozen IVF cycles between 2007 and 2012 (N = 249,630).
Intervention(s): None.
Main Outcome Measure(s): First trimester pregnancy loss.
Result(s): A diagnosis of uterine factor was associated with an increased risk of loss in women aged 40 years and younger (<30 years: adjusted risk ratio (aRR) = 1.24, 95% confidence interval (CI) 1.04–1.48; 30–34 years: aRR = 1.27, 95% CI 1.17–1.38; 35–37 years: aRR = 1.12, 95% CI 1.03–1.21; 38–40 years: aRR = 1.08, 95% CI 1.01–1.17). There was an increased risk of loss in women with diminished ovarian reserve aged 30–34 years (aRR = 1.08, 95% CI 1.01–1.15) and in women with ovulatory dysfunction younger than 35 years (<30 years: aRR = 1.12, 95% CI 1.05–1.19; 30–34 years: aRR = 1.07, 95% CI 1.02–1.13). There was an increased risk of loss after frozen ETs versus fresh among women younger than 38 years, but this remained significant in the subanalysis of similar quality embryos only in women younger than 30 years (aRR = 1.16, 95% CI 1.04–1.32).
Conclusion(s): Uterine factor had the largest increased risk of loss among infertility diagnoses, although the magnitudes of all risks were small. When transferring embryos of similar quality, the risks of loss were similar between fresh and frozen cycles. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Miscarriage, early pregnancy loss, in vitro fertilization (IVF), infertility

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An estimated 30% of pregnancies end in miscarriage (1). Early pregnancy loss can not only perpetuate feelings of guilt and isolation (2), but also have a detrimental effect on women's emotional health (3). This sorrow is often amplified in women with infertility, many of whom have undergone invasive fertility treatment for years and report intense grief, anxiety, and feelings of powerlessness (4).

Understanding risk factors that contribute to early pregnancy loss can aid in counseling and possibly guide treatment. Although many early losses are unrecognized (1), pregnancies conceived with assisted reproductive technology (ART) are typically more closely monitored than spontaneous pregnancies and allow for a more detailed examination of risks. Known risk factors are advancing maternal age, multiple prior losses, or certain coagulopathic or uterine anatomic factors (5). There may also be miscarriage risks specific to women with infertility, including the infertility diagnosis that necessitated reproductive treatment, such as diminished ovarian reserve (6–8), ovulatory dysfunction (9–12), tubal factor (13, 14) or uterine factor, which includes fibroids, adhesions, and congenital uterine anomalies (15, 16). These diagnoses, respectively, account for 31%, 14%, 14%, and 6% of the causative etiologies of infertility (17). IVF cycle-dependent factors, such as transferring an embryo

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during a fresh versus a frozen cycle, may also modify the risk of miscarriage (18–20).

The objectives of this study were to determine whether there are early pregnancy loss risks specific to women who have conceived with IVF in the United States by analyzing a large retrospective cohort of pregnancies from the National ART Surveillance System. We explored significant risk factors and further investigated the impact of infertility diagnoses and ET environments (i.e., fresh vs, frozen) on the risk of early loss.

MATERIALS AND METHODS

The data in this study are from the National ART Surveillance System, the Centers for Disease Control and Prevention's web-based surveillance system used to collect information on ART cycles conducted in the United States (17). It is estimated that the surveillance system captures >97% of ART cycles (21), procedures in which oocytes or embryos are handled in a laboratory with the intent to establish a pregnancy. Assisted reproductive technology includes IVF, gamete intrafallopian transfer, and zygote intrafallopian transfer (ZIFT), although >99% of ART cycles currently performed are IVF (21). Data are cycle-specific and include patient demographics, parity, infertility diagnosis, stimulation information, and, if pertinent, obstetric outcome. The data are verified by the medical director of each contributing clinic. In addition, annual data validation are performed for a random sample of clinics submitting data to the National ART Surveillance System (7%–10%) by comparing reported data with medical record charts (21).

We analyzed clinical pregnancies that resulted from fresh and frozen autologous IVF cycles begun between 2007 and 2012. Because pregnancy outcome was the outcome of interest in this study, we only included cycles with known pregnancy outcomes. Cycles were excluded if there was use of a gestational carrier, use of preimplantation genetic diagnosis/screening, or a transfer day other than 2, 3, 5, or 6. We were able to link frozen cycles to previous fresh oocyte retrievals begun after 2004, allowing for the calculation of maternal age at oocyte retrieval, one of the largest determinants of miscarriage (21). Frozen cycles were excluded that could not be linked to a fresh retrieval, had no prior ART cycles, or were linked to a fresh cycle reporting zero embryos cryopreserved or had no ET within the 365 days after the retrieval. Because embryo developmental stage at transfer is not collected for frozen cycles, we assumed the embryo stage at transfer for a frozen cycle was the same as that for the linked fresh cycle. There were 59,738 pregnancies achieved from frozen ETs meeting our study criteria, and we were able to link 45,660 to an originating fresh cycle (76%).

The outcome of interest was first trimester pregnancy loss, which was defined as loss of the entire gestation before 14 weeks of gestation. Clinical pregnancy was defined as a gestational sac(s) seen on ultrasound with or without a fetal pole or cardiac activity. Biochemical and ectopic pregnancies (EP) were excluded. Fresh cycles are those in which embryo(s) are transferred after an oocyte retrieval and fertilization with no interval embryo freezing. Frozen cycles involve the transfer of embryo(s) that had been previously frozen after the initial retrieval and fertilization, and then thawed for transfer in a later menstrual cycle.

Log binomial regression using generalized estimating equations with an independent correlation matrix to account for clustering by clinic was performed to characterize the relationship between first trimester pregnancy loss and maternal characteristics, IVF cycle characteristics, and pregnancy outcome. Multivariable log binomial regression, also using generalized estimating equation, was then performed to compare risk of first trimester pregnancy loss in fresh cycles among different infertility diagnoses, including male factor, ovulatory dysfunction, which includes polycystic ovarian syndrome (PCOS), diminished ovarian reserve (DOR), endometriosis, tubal factor, and uterine factor. Risk of first trimester pregnancy loss was compared between cycles with and without the infertility diagnosis in question (e.g., male factor vs. no male factor), allowing for concomitant infertility diagnoses. The model included indicators for each infertility diagnosis, female age group (<30, 30–34, 35–37, 38–40, >40 years), and an interaction between each infertility diagnosis and age group to produce risk ratios for each infertility diagnosis by age group. We also controlled for number of prior miscarriages, number of prior births, number of prior ART cycles, the use of assisted hatching, the number of supernumerary embryos cryopreserved, and the number of fetal heartbeats on first ultrasound, all selected using backward elimination. Two variables that were not considered for inclusion in the multivariable models due to a large percentage of data missing were race (35.7% missing) and body mass index (BMI) (23.6% missing). Unadjusted risk ratios (RRs), adjusted risk ratios (aRRs), and 95% confidence intervals (CIs) were calculated.

Multivariable log binomial regression, using generalized estimating equation, was also performed to calculate RRs, aRRs, and 95% CIs to compare the risk of first trimester pregnancy loss between fresh and frozen ETs. The model included cycle type (fresh/frozen), age group (<30, 30–34, 35–37, 38–40, >40 years), and an interaction between cycle type and age group to produce risk ratios for cycle type by age group. Other characteristics controlled for, selected using backward elimination, included number of prior miscarriages, number of prior births, number of prior ART cycles, the infertility diagnoses of ovulatory dysfunction, diminished ovarian reserve, and uterine factor, number of oocytes retrieved, number of embryos transferred, the use of assisted hatching, the number of embryos cryopreserved, the number of fetal heartbeats on first ultrasound, and the reporting year. Intracytoplasmic sperm injection (ICSI) and embryo stage at transfer, which were not available for frozen cycles, were excluded from these analyses. Race and BMI were again excluded for consideration in the multivariable models due to a large amount of missing data.

Given that patients typically transfer the "highest quality" embryo with their fresh cycle (typically their first transfer), we attempted to correct for embryo quality with a subanalysis that compared fresh and frozen cycles among first transfer cycles only. We restricted frozen cycles to include only those occurring directly after an originating

fresh cycle with no ET. In other words, the embryo(s) transferred during the frozen cycle were the first embryos transferred from the originating retrieval. Included frozen cycles were restricted to those occurring within 365 days of the original retrieval and that had at least one embryo cryopreserved from the fresh retrieval.

All analyses were conducted with SAS version 9.3 (SAS Institute, Inc.). This study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention.

RESULTS

We analyzed 249,630 intrauterine pregnancies (IUP) resulting from IVF cycles performed between 2007 and 2012, including 203,970 fresh cycles and 45,660 linked frozen cycles. Of all the pregnancies, 37,445 (15%) ended in a first trimester loss, 204,333 (81%) resulted in a live birth and the remainder ended in a second or third trimester pregnancy loss (5,435, 2%), therapeutic abortion (2,398, 0.1%), or maternal death (19, <0.01%).

Patient-specific factors (Table 1) associated with an increased risk of first trimester pregnancy loss included increasing maternal age at the time of oocyte retrieval and a higher number of prior pregnancies, prior spontaneous abortions, prior births, and/or prior ART cycles. Infertility diagnoses associated with the highest risk of early pregnancy loss included uterine factor and DOR. Cycle-specific factors that were associated with an increased risk of early loss included the transfer of a frozen embryo, a lower number of oocytes retrieved, absence of ovarian hyperstimulation, transfer of cleavage-stage embryos (day 2/3), the use of assisted hatching, and the cryopreservation of "0" supernumerary embryos. The transfer of two embryos was associated with the lowest risk of first trimester pregnancy loss (12.6%), followed by one embryo (16.8%), three embryos (17.2%), and four or more embryos (24.1%). Although there appeared to be an increased risk of loss with increasing BMI and race/ethnicity other than non-Hispanic white, statistical testing was not performed for these two variables due to the amount of missing data.

The adjusted risk of first trimester pregnancy loss was significantly higher for women aged 40 years and younger with uterine factor infertility compared with those without uterine factor (<30 years: aRR = 1.24, 95% CI 1.04–1.48; 30–34 years: aRR = 1.27, 95% CI 1.17–1.38; 35–37 years: aRR = 1.12, 95% CI 1.03–1.21; 38–40 years: aRR = 1.08, 95% CI 1.01–1.17) (Table 2). The adjusted risk of loss was also higher among 30- to 34-year-old women with DOR (aRR = 1.08, 95% CI 1.01–1.15), 38- to 40-year-old women with endometriosis (aRR = 1.08, 95% CI 1.01–1.14), and among women younger than 35 years with ovulatory dysfunction (<30 years: aRR = 1.12, 95% CI 1.05–1.19; 30–34 years: aRR = 1.07, 95% CI 1.02–1.13) compared with those without these diagnoses. The diagnoses of tubal factor and male factor infertility did not impart an increased risk for early loss.

The risk of first trimester pregnancy loss after a transfer during frozen cycles, compared with fresh, was significantly higher for women aged 40 years and younger, although the magnitude of risk varied by age group (Table 3). When adjusted for other predictors of early loss, the increased risk for frozen cycles remained significant only for women younger than 38 years (<30 years: aRR = 1.37, 95% CI 1.29–1.44; 30–34 years: aRR = 1.23, 95% CI 1.18–1.27; 35–37 years: aRR = 1.14, 95% CI 1.09–1.19). In the subgroup analysis comparing risk of early loss when transferring embryos of similar quality (Table 4), the increased risk for frozen cycles remained significant only in women younger than 30 years of age (aRR = 1.16, 95% CI 1.04–1.32). In women older than 40 years, the risk of early loss was lower when transferring frozen embryos versus fresh (aRR = 0.89, 95% CI 0.79–0.99).

DISCUSSION

The magnitudes of risk for all infertility diagnoses found in this study for first trimester pregnancy loss were likely of limited clinical significance. The risk for women with uterine factor, with adjusted relative risks that ranged from 1.08–1.27 in women younger than 40 years, was the highest among the diagnoses. These findings are comparable to those in other studies in women with anatomic abnormalities, including fibroids and intrauterine adhesions (15, 16), and are likely due to cavity distortion and alteration of uterine perfusion and myometrial function. The risk for women with endometriosis, found in women aged 38–40 years only (aRR = 1.08), and absent risk in couples with male factor infertility are similar to that found in prior literature (22–24). The marginally increased risks found for some women with DOR and ovulatory dysfunction and the absent risk for women with tubal factor are discrepant with some prior publications indicating that these women are at a much higher risk for early loss (6, 7, 10, 13).

We found a statistically increased risk for early loss only in women with ovulatory dysfunction younger than 35 years. In women younger than 30 years, their risk of loss was 1.12 times higher than in women without ovulatory dysfunction. In women aged 30–34 years, the risk was 1.07 times higher. Women with PCOS, however, are more likely to be obese, a potential confounding influence on miscarriage risk (9). Our findings corroborate recent studies that did not find nonobese women with PCOS to have a higher risk for miscarriage (11) or did not find a risk after adjusting for fertility medication use (12) or BMI (9), for which we were unable to adjust.

Other studies have concluded that women with DOR are also at a higher risk for miscarriage (6, 7). Our findings, statistically significant only in women aged 30–34 years (aRR = 1.08), are of questionable clinical significance. These findings agree with other investigators who have not found young women with DOR to be at higher risk for early loss if good quality embryos are transferred (8). Another recent study (25) found similar miscarriage rates in women with a wide range of antral follicle counts undergoing therapeutic donor insemination. These findings and ours suggest that female age, almost irrespective of ovarian reserve, impacts miscarriage risk.

TABLE 1

First trimester pregnancy loss by maternal characteristics in fresh and frozen autologous IVF cycles from 2007 to 2012.

Characteristic	No. of IUP	No. of first trimester losses (% of all pregnancies)	*P* value
Total	249,630	37,445 (15)	
Maternal age (y) at oocyte retrieval[a]			<.0001
<30	43,163	4,213 (9.8)	
30–34	96,198	10,814 (11.2)	
35–37	55,856	8,186 (14.7)	
38–40	39,131	8,606 (22.0)	
>40	15,282	5,626 (36.8)	
Race/ethnicity[b]			
Non-Hispanic white	118,482	16,607 (14.0)	
Non-Hispanic black	9,735	1,802 (18.5)	
Asian/Pacific Islander	17,990	3,059 (17.0)	
Hispanic	14,003	2,160 (15.4)	
Other	345	55 (15.9)	
Body mass index (kg/m^2)[b]			
<20	22,751	3,175 (14.0)	
20–24.9	91,686	13,071 (14.3)	
25.0–29.9	44,007	6,763 (15.4)	
≥30	32,176	5,630 (17.5)	
No. of prior pregnancies[a]			<.0001
0	110,062	14,503 (13.2)	
1	70,686	10,865 (15.4)	
≥2	68,203	11,998 (17.6)	
No. of prior spontaneous abortions[a]			<.0001
0	173,744	23,990 (13.8)	
1	49,679	8,523 (17.2)	
≥2	24,779	4,751 (19.2)	
No. of prior births[a]			<.0001
0	173,692	25,594 (14.7)	
1	58,250	8,911 (15.3)	
≥2	16,572	2,776 (16.8)	
No. of prior ART cycles[a]			<.0001
0	126,941	16,448 (13.0)	
1	62,975	10,178 (16.2)	
≥2	59,673	10,812 (18.1)	
Infertility diagnosis			
Male factor[a]			<.0001
Yes	101,683	14,301 (14.1)	
No	147,947	23,144 (15.6)	
Ovulatory dysfunction[a]			<.0001
Yes	46,367	6,316 (13.6)	
No	203,263	21,129 (15.3)	
Diminished ovarian reserve[a]			<.0001
Yes	35,615	7,834 (22.0)	
No	214,015	29,611 (13.8)	
Endometriosis[a]			<.0001
Yes	29,111	4,027 (13.8)	
No	220,519	33,418 (15.2)	
Uterine factor[a]			<.0001
Yes	10,409	2,127 (20.4)	
No	239,221	35,318 (14.8)	
Tubal factor[a]			.5167
Yes	40,685	6,156 (15.1)	
No	208,945	31,289 (15.0)	
Other factor[a]			<.0001
Yes	27,171	4,603 (16.9)	
No	222,459	32,842 (14.8)	
Unknown factor[a]			.0019
Yes	36,561	5,212 (14.3)	
No	213,069	32,233 (15.1)	
Cycle type[a]			<.0001
Fresh	203,970	29,199 (14.3)	
Frozen	45,660	8,246 (18.1)	
No. of oocytes retrieved[a,c]			<.0001
<5	13,887	2,993 (21.6)	
5–9	57,810	9,704 (16.8)	
10–19	119,644	16,795 (14.0)	
20–29	44,811	6,124 (13.7)	
≥30	13,454	1,825 (13.6)	
Ovarian hyperstimulation (fresh cycles only)[a]			<.0001
Yes	2,956	275 (9.3)	
No	201,014	28,924 (14.4)	
No. of embryos transferred[a]			<.0001
1	30,645	5,133 (16.8)	
2	148,509	18,774 (12.6)	
3	50,020	8,614 (17.2)	
≥4	20,442	4,917 (24.1)	
Use of intracytoplasmic sperm injection[c,d]			.5679
Yes	178,265	26,626 (14.9)	
No	65,246	9,848 (15.1)	
Embryo stage at transfer[c,e]			<.0001
Day 2/3	118,430	19,915 (16.8)	
Day 5/6	119,784	15,645 (13.1)	
Use of assisted hatching[a]			<.0001
Yes	94,374	17,472 (18.5)	
No	155,256	19,973 (12.9)	
No. of supernumerary embryos cryopreserved[a,c]			<.0001
0	104,332	18,072 (17.3)	
1–2	47,629	6,549 (13.8)	
3–4	40,322	5,349 (13.3)	
≥5	56,745	7,411 (13.1)	
No. of fetal heartbeats on first ultrasound[a]			<.0001
0	16,592	15,832 (95.4)	
1	157,723	19,025 (12.1)	
2	67,754	1,762 (2.6)	
≥3	6,785	122 (1.8)	
Reporting year[a]			.0006
2007	37,448	5,264 (14.1)	
2008	41,308	6,167 (14.9)	
2009	41,396	6,325 (15.3)	
2010	42,151	6,273 (14.9)	
2011	42,376	6,602 (15.6)	
2012	44,951	6,814 (15.2)	

Note: ART = assisted reproductive technology; IUP = intrauterine pregnancy. Data are n (%) unless otherwise specified.

[a] Missing <1%.

[b] >20% missing, no statistical testing conducted due to large amount of unavailable data.

[c] For frozen cycles included, data from original fresh cycles to which cycle is linked.

[d] Missing 2.5%.

[e] Missing 4.6%.

Hipp. Early pregnancy loss after IVF. Fertil Steril 2015.

Unlike prior studies (13, 14), we did not find tubal factor to confer an increased risk of early loss. One possible explanation is our inclusion of more recent calendar years. As more literature suggests that untreated hydrosalpinges increase miscarriage risk and adverse perinatal outcomes (26), tubal occlusion or removal before IVF may be more common. In addition, the two prior studies used different comparison groups, male factor (13) and unexplained infertility (14). Our comparison group was women without tubal factor, allowing for concomitant diagnoses.

Recently, studies have suggested benefit to a "freeze-all" policy for embryos (27), arguing that ET into a more physiologic endometrial environment in frozen cycles increases pregnancy rates (PRs) and decreases ectopic pregnancy (EP) risks and poor perinatal outcomes (19,28–30). It is

TABLE 2

Risks of first trimester pregnancy loss by infertility diagnosis in fresh autologous IVF cycles, stratified by maternal age.

	Age (y), < 30		Age (y), 30–34		Age (y), 35–37		Age (y), 38–40		Age (y), > 40	
Variable	**% of losses[a]**	**aRR (95% CI)**	**% of losses[a]**	**aRR (95% CI)**	**% of losses[a]**	**aRR (95% CI)**	**% of losses[a]**	**aRR (95% CI)**	**% of losses[a]**	**aRR (95% CI)**
Male factor										
Yes	8.3	1.05 (0.99–1.11)	9.8	0.99 (0.95–1.03)	13.7	1.01 (0.97–1.05)	21.5	1.03 (0.99–1.07)	37.1	0.97 (0.93–1.02)
No	8.2	1	10.2	1	13.7	1	21.6	1	37.1	1
Ovulatory dysfunction										
Yes	8.9	1.12 (1.05–1.19)	10.6	1.07 (1.02–1.13)	13.9	1.02 (0.96–1.07)	20.8	1.02 (0.96–1.08)	37.0	1.02 (0.94–1.11)
No	8.0	1	9.9	1	13.6	1	21.6	1	37.1	1
Diminished ovarian reserve										
Yes	8.8	1.00 (0.87–1.15)	11.5	1.08 (1.01–1.15)	14.7	1.02 (0.97–1.07)	23.3	1.02 (0.99–1.06)	38.4	1.04 (0.99–1.10)
No	8.2	1	9.9	1	13.5	1	20.8	1	35.9	1
Endometriosis										
Yes	7.8	1.00 (0.91–1.01)	10.1	1.00 (0.94–1.05)	13.9	1.01 (0.95–1.07)	21.8	1.08 (1.01–1.14)	39.8	1.09 (0.98–1.20)
No	8.3	1	10.0	1	13.6	1	21.5	1	37.0	1
Tubal factor										
Yes	8.4	1.08 (0.98–1.18)	10.2	1.02 (0.97–1.07)	13.6	0.98 (0.93–1.03)	22.0	1.03 (0.98–1.08)	37.5	1.01 (0.95–1.08)
No	8.2	1	10.0	1	13.7	1	21.4	1	37.1	1
Uterine factor										
Yes	11.1	1.24 (1.04–1.48)	13.6	1.27 (1.17–1.38)	16.7	1.12 (1.03–1.21)	25.5	1.08 (1.01–1.17)	40.9	1.04 (0.95–1.13)
No	8.2	1	9.9	1	13.5	1	21.3	1	36.9	1

Note: Models were adjusted for number of prior miscarriages, number of prior births, number of prior ART cycles, the use of assisted hatching, the number of supernumerary embryos cryopreserved, and the number of fetal heartbeats on first ultrasound. aRR = adjusted risk ratio; ART = assisted reproductive technology; CI = confidence interval.

[a] % of first trimester losses in clinical pregnancies.

Hipp. Early pregnancy loss after IVF. Fertil Steril 2015.

TABLE 3

Risk of first trimester pregnancy loss among pregnancies after transfer of frozen versus fresh embryos, stratified by maternal age at oocyte retrieval.

	Fresh embryos	Frozen embryos		
Maternal age (y)	First trimester losses, n (%)	First trimester losses, n (%)	RR (95% CI)[a]	aRR (95% CI)[a]
<30	2,729 (8.2)	1,484 (14.9)	1.82 (1.70–1.94)	1.37 (1.29–1.44)
30–34	7,687 (10.0)	3,127 (16.1)	1.61 (1.54–1.69)	1.23 (1.18–1.27)
35–37	6,286 (13.7)	1,900 (19.3)	1.41 (1.34–1.48)	1.14 (1.09–1.19)
38–40	7,337 (21.5)	1,269 (25.1)	1.16 (1.08–1.26)	1.05 (0.99–1.11)
>40	5,160 (37.1)	466 (33.6)	0.90 (0.80–1.02)	0.96 (0.90–1.03)

Note: Models were adjusted for number of prior miscarriages, prior births, and prior ART cycles, the infertility diagnoses of ovulatory dysfunction, DOR, and uterine factor, number of oocytes retrieved, number of embryos transferred, the use of assisted hatching, the number of embryos cryopreserved, the number of fetal heartbeats on first ultrasound, and the reporting year. aRR = adjusted risk ratio; ART = assisted reproductive technology; CI = confidence interval; DOR = diminished ovarian reserve; RR = risk ratio.

[a] Reference group is fresh ET.

Hipp. Early pregnancy loss after IVF. Fertil Steril 2015.

hypothesized that supraphysiologic estrogen (E) levels in fresh cycles alters endometrial receptivity through modifications of genetic expression and downstream morphological changes (31, 32). Early pregnancy loss, however, was not included as a primary outcome in these studies, leaving a potential knowledge gap. Two studies (18, 20), which did assess first trimester loss as a secondary outcome in fresh versus frozen cycles, found no difference in loss rates. These analyses, however, possibly lacked statistical power with only 33 and 52 miscarriage events included. In our study, we were able to analyze a large cohort of first trimester losses. Although we found a higher loss risk after frozen ETs in women younger than 38 year old, our subanalysis (first transfer per retrieval) that attempted to correct for embryo quality found only an increased risk of early pregnancy loss in women younger than 30 years, which was not likely clinically significant.

Our study's findings are strengthened by the large cohort of women and breadth of available patient and cycle characteristic data. We controlled for many factors that potentially affect loss risk, such as maternal age, parity, and number of embryos transferred.

The study was limited by some data availability. Embryo stage at transfer was unavailable for the frozen cycles and patients who transfer cleavage embryos in fresh cycles may culture their embryos to the blastocyst stage for frozen transfers. Transfer of blastocyst embryo(s) has a lower miscarriage risk (33), which could potentially decrease the adjusted relative risks found in the analyses of frozen versus fresh ETs. Incomplete data were available for race/ethnicity and BMI, known contributors to miscarriage. Although not included in the multivariable analysis, a secondary analysis including these two variables did not show differences in the results (data not presented). Last, although the data are validated by the medical director of each clinic, inclusion criteria for each diagnosis can be broad and certain diagnoses, such as endometriosis, likely underdiagnosed so women are labeled as having unexplained infertility. Given that clinical decisions in IVF are often made based on the information available (e.g., without a laparoscopy), our findings are still helpful for clinical decision-making.

Our study characterizes early pregnancy loss risks specific to infertile women conceiving with IVF. Fortunately, no infertility diagnosis, apart from uterine factor, imparts a large increased risk. Our findings provide reassurance to women that the infertility diagnosis, which has prompted IVF, does not increase their chance of early loss. In addition, transfer of similar quality embryos in fresh and frozen cycles has

TABLE 4

Risk of first trimester pregnancy loss among pregnancies after transfer of frozen versus fresh embryos, stratified by maternal age at oocyte retrieval, subgroup analysis.

	Fresh embryos	Frozen embryos		
Maternal age (y)	First trimester losses, n (%)	First trimester losses, n (%)	RR (95% CI)[a]	aRR (95% CI)[a]
<30	2,729 (8.2)	199 (12.0)	1.46 (1.26–1.69)	1.16 (1.04–1.32)
30–34	7,687 (10.0)	396 (13.1)	1.31 (1.17–1.47)	1.08 (0.98–1.18)
35–37	6,286 (13.7)	271 (16.3)	1.19 (1.06–1.33)	1.07 (0.96–1.18)
38–40	7,337 (21.5)	240 (21.6)	1.00 (0.88–1.14)	0.96 (0.87–1.05)
>40	5,160 (37.1)	136 (32.2)	0.87 (0.74–1.02)	0.89 (0.79–0.99)

Note: Frozen cycles restricted to those occurring directly after a fresh cycle during which no transfer was performed (i.e., first ET from originating fresh cycle). Models were adjusted for number of prior miscarriages, prior births, and prior ART cycles, the infertility diagnoses of ovulatory dysfunction, DOR, and uterine factor, number of oocytes retrieved, number of embryos transferred, the use of assisted hatching, and the number of fetal heartbeats on first ultrasound. aRR = adjusted risk ratio; ART = assisted reproductive technology; CI = confidence interval; DOR = diminished ovarian reserve; RR = risk ratio.

[a] Reference group is fresh ET.

Hipp. Early pregnancy loss after IVF. Fertil Steril 2015.

similar early pregnancy loss risks, allowing women and their physicians to transfer fresh or frozen embryos based on other concerns.

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