THE ASSOCIATION BETWEEN TYPE OF PROGESTERONE SUPPLEMENTATION AND MISCARRIAGE RISK IN WOMEN WITH A POSITIVE PREGNANCY TEST FOLLOWING EMBRYO TRANSFER: A RETROSPECTIVE COHORT STUDY

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BACKGROUND

In both fresh and frozen embryo transfers (ETs) after in vitro fertilization (IVF), exogenous progesterone is required to overcome the deficient luteal phase of the former and the absent natural luteal phase of the latter and induce appropriate endometrial changes in preparation for implantation and support the first weeks of pregnancy. The vaginal (PV) and intramuscular (IM) routes of progesterone have been most heavily studied from the available options. The PV route which requires one to three applications per day, versus the IM route which requires only one, is still the preferred route by patients due to lower discomfort and ease of administration (1, 2). Numerous studies comparing clinical outcomes with PV versus IM progesterone for luteal phase support (LPS), in both fresh and frozen cycles, compared similar formulations of progesterone; however, doses of progesterone, study design, patient populations and outcome definitions varied. The most recent meta-analysis of 15 randomized controlled trials (RCTs) showed no difference in live birth rate or miscarriage risk between the two routes when both fresh and frozen ETs were studied together and separately (3). For frozen cycles specifically, results of an interim analysis of a recent large well-designed three-arm RCT comparing IM progesterone alone to PV progesterone alone to a combination of daily PV progesterone with IM progesterone every third day revealed a higher clinical pregnancy loss risk and lower clinical pregnancy risk in the group of patients receiving only vaginal progesterone compared to the other two groups (4). A second less well designed RCT showed neutral results (5). Miscarriage was not the primary outcome in any study. In all studies, the type and route of progesterone used was consistent throughout the entire luteal phase and early pregnancy.

OBJECTIVE

The aim of this study was to investigate the association between type of progesterone supplementation after a positive pregnancy test and miscarriage in IVF, and to determine if switching from IM progesterone to PV progesterone after a positive pregnancy test is associated with higher miscarriage risk.

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MATERIALS AND METHODS

This was a retrospective cohort study in a private university-affiliated fertility clinic in Montreal, Canada. Women aged 18 to 50 at the time of ET, with a positive pregnancy test following their ET between 2013 and 2016, were included. Only first IVF pregnancies were included. Biochemical pregnancies as well as pregnancies from oocyte donor, surrogacy, natural fresh or natural frozen cycles were excluded. A total of 1988 women with complete data on exposure and outcome were included in the analysis. Two groups of women were studied: those who stayed on IM progesterone following a positive pregnancy test and those who switched to PV progesterone after a positive test. This sample size provides 84% power, at the 0.05 significance level, to detect a difference of 6% in miscarriage risk. The main outcome measured was the risk of miscarriage < 24 weeks gestation as a proportion of non-biochemical pregnancies after fresh or frozen ET. A univariate analysis was performed to test the association between the two types of progesterone and risk of miscarriage, as well as a multivariable logistics regression controlling for age, BMI, antral follicle count, parity, prior miscarriages, duration and cause of infertility, prior failed ETs, number of good quality embryos in original cycle, fresh vs frozen ET, stage of embryo(s) transferred, number of embryos transferred.

RESULTS

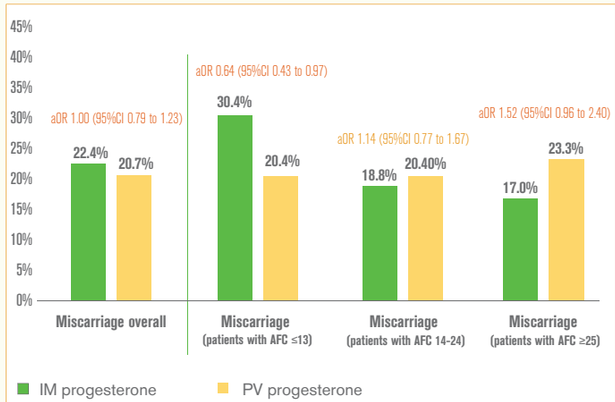
With regards to the primary outcome, miscarriage risk < 24 weeks, 22.4% (274/1221) of patients in the IM progesterone group experienced a miscarriage compared with 20.7% (159/767) in the vaginal progesterone group. The mean gestational age at which the miscarriage took place was similar between the groups (8.4 ± 2.2 weeks in IM group, 8.5 ± 3.3 weeks in PV groups; p=0.61). Significant associations were found between miscarriage and age at oocyte pickup, BMI, AMH, AFC as a categorical variable, parity, prior number of miscarriages, prior failed ETs as a binary variable, type of ET (fresh or frozen), and number and stage of embryo(s) transferred. A univariate analysis revealed an unadjusted OR of 0.90 (95%CI 0.73 to 1.13, p=0.369) for the association between progesterone type and miscarriage. Results of a multivariable logistic regression model, adjusting for effect modification by antral follicle count (AFC) is presented in figure 1. When the main association was tested in fresh and frozen cycles separately, no association was found in either of these groups, although this analysis was likely underpowered.

Table 1: Baseline patient characteristics by progesterone type and associations with type of progesterone.

	IM prog. N=122		PV prog. N=767		p-value*
Age at oocyte pickup (mean ± SD)	34.1	(±4.5)	33.9	(±4.5)	0.214
20-29 (n, %)	237	(19.4)	157	(20.5)	
30-34	442	(36.2)	281	(36.6)	0.858
35-39	414	(33.9)	256	(33.4)	
≥ 40	128	(10.5)	73	(9.5)	
BMI, kg/m2 (mean, SD)	25.7	(±5.2)	25.3	(±5.1)	0.077
<18.5	32	(2.6)	23	(3.0)	
18.5-24.9	593	(48.6)	407	(53.1)	
25-29.9	328	(26.9)	193	(25.2)	0.274
>30	251	(20.6)	140	(18.3)	
Missing	17	(1.4)	4	(0.5)	
Antral follicle count (mean ± SD)	21.2	(±13.3)	21.0	(±13.2)	0.745
≤13 (n, %)	355	(29.1)	231	(30.1)	
14-24	446	(36.5)	290	(37.8)	
≥25	342	(28.0)	199	(26.0)	0.572
Missing	78	(6.4)	47	(6.13)	
Parity (mean ± SD)	0.41	(±0.77)	0.42	(±0.65)	0.852
None (n, %)	839	(68.7)	504	(65.7)	
≥ 1	374	(30.6)	262	(34.2)	0.118
Missing	8	(0.7)	1	(0.1)	
Previous miscarriages	0.42	(±0.92)	0.29	(0.67)	0.001
None (n, %)	900	(73.7)	609	(79.4)	
≥ 1	316	(25.9)	158	(20.6)	0.006
Missing	5	(0.4)	0	(0.0)	
Duration of infertility, y (mean, ± SD)	2.7	(±2.4)	2.8	(±2.3)	0.754
≤ 2 years (n, %)	655	(53.6)	418	(54.5)	
> 2 years	539	(44.1)	334	(43.6)	0.753
Missing	27	(2.2)	15	(1.96)	
Cause of infertility (n, %)					
Tubal/severe endometriosis	136	(11.1)	88	(11.5)	0.885
Male factor	421	(34.5)	284	(37.0)	
Unexplained	447	(36.6)	266	(34.7)	
Ovulatory dysfunction	104	(8.5)	62	(8.1)	
Mixed	75	(6.1)	43	(5.6)	
Other	35	(2.9)	22	(2.9)	
Missing	3	(0.3)	2	(0.3)	
Prior failed ETs (mean ± SD)	0.92	(±1.3)	0.68	(±1.2)	<0.001
None (n, %)	647	(53.0)	491	(64.0)	
≥1	571	(46.8)	276	(36.0)	<0.001
Missing	3	(0.3)	0	(0.0)	
No. good quality embryos produced in original cycle (mean ± SD)	3.35	(2.1)	3.21	(1.9)	0.140
1-2 (n, %)	471	(38.6)	311	(40.6)	0.376
≥ 3	749	(61.3)	455	(59.3)	
Missing	1	(0.1)	1	(0.1)	
Type of ET (n, %)					
Fresh	738	(60.4)	507	(66.1)	0.011
Frozen	483	(39.6)	260	(33.9)	
No. embryo(s) transferred (mean ± SD)	1.20	(±0.4)	1.18	(±0.4)	0.304
1 (n, %)	1001	(82.0)	649	(84.2)	
2	198	(16.2)	100	(13.0)	0.119
3	22	(1.8)	18	(2.4)	
Stage of embryo(s) transferred (n, %)					
Cleavage stage	549	(45.0)	354	(46.2)	0.604
Blastocyst	672	(55.0)	413	(53.9)	
Miscarriage	274	(22.4)	159	(20.7)	0.370

IM prog: intramuscular progesterone; PV prog: vaginal progesterone; BMI: body mass index; ET: embryo transfer; AMH: anti-mullerian hormone; FSH : follicle stimulating hormone
*p-value from chi-squared test for categorical variables, or t-test for continuous variables
For variables with no "missing" category there are no missing values.

Figure 1: Clinical outcomes by type of progesterone, overall and by AFC



Complete case analysis multivariable logistic regression (9.8% of records dropped due to missing values, n=1793); aOR: adjusted odds ratio, adjused for age, BMI, antral follicle count (AFC), parity, prior miscarriages, duration and cause of infertility, prior failed ETs, number of good quality embryos in original cycle, fresh vs frozen ET, stage of embryo transferred, number of embryos transferred.

CONCLUSIONS

This is the first study to our knowledge evaluating the effect of switching from one type of progesterone to another during the same cycle. Results demonstrate that switching from IM to PV progesterone after a positive pregnancy test following an ET is not associated with a change in miscarriage risk, and this even after adjusting for potential confounders. An interesting finding is that of effect modification by level of AFC: among patients with <13 antral follicles, users of PV progesterone experiences a lower odds of miscarriage (aOR 0.64, 95%CI 0.43 to 0.97). The direction of this OR shifts in the higher AFC category. A hypothesis is that patients with a lower ovarian reserve have less endogenous estradiol produced during stimulation and may require less progesterone to sustain pregnancy.

Considering that IM progesterone imposes substantial discomfort, this study offers clinicians and patients comforting results and some flexibility in treatment protocols. This study is limited by its retrospective design, and further prospective studies are necessary to corroborate results, and to investigate this association in different patient or cycle subgroups, such as by fresh or frozen cycles or by level of ovarian reserve.