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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

The association between the type of progesterone supplementation and miscarriage risk in women who have had a positive pregnancy test following embryo transfer: a retrospective cohort study

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Abstract

Purpose The purpose of this study was to identify if switching from intramuscular (IM) to vaginal progesterone compared to staying on IM progesterone after a positive pregnancy test following embryo transfer (ET) is associated with miscarriage risk.

Methods A retrospective cohort study was performed in a private university-affiliated fertility clinic and included women aged 18–50 years with a positive pregnancy test following ET. The two groups studied were: women who stayed on IM progesterone following a positive pregnancy test and those who switched to vaginal progesterone after a positive test. The main outcome measured was risk of miscarriage < 24 weeks gestation as a proportion of non-biochemical pregnancies.

Results 1988 women were included in the analysis. Among the baseline characteristics, the presence of prior miscarriages as well as prior failed ETs, and frozen cycles (vs fresh) as type of transfer were associated with IM progesterone use (p values ≤ 0.01). As per 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 (OR 0.90; 95% CI 0.73–1.13). A multivariable logistic regression model revealed an adjusted OR (aOR) of 0.97 (95% CI 0.77–1.22).

Conclusion This study suggests that switching from IM to vaginal progesterone after a positive pregnancy test following an ET is not associated with miscarriage risk. Considering that IM progesterone imposes substantial discomfort, this study offers reassurance and some flexibility in treatment protocols. Further prospective studies are necessary to corroborate the results of this study.

Keywords In vitro fertilization · Intramuscular progesterone · Vaginal progesterone · Miscarriage · Luteal phase support

What does this study add to the clinical work

This is the first study to our knowledge evaluating the effect of switching luteal support from intramuscular to vaginal progesterone in the same treatment cycle. This study can reassure clinicians and patients that this switch is unlikely to be detrimental with regard to miscarriage.

Introduction

In IVF treatment protocols, exogenous progesterone is used to overcome the luteal phase deficiency caused by disturbed feedback mechanisms along the hypothalamic–pituitary–ovarian axis, which prohibits endogenous progesterone secretion in both fresh stimulated IVF cycles and substituted frozen embryo transfer (ET) cycles, both by different mechanisms [1, 2]. Among available routes of administration for progesterone, the vaginal and intramuscular (IM) routes are most popular and have been most heavily studied. The vaginal route which requires one to three applications per day, versus the IM route which requires only one, is the preferred route by patients due to lower discomfort and ease of administration [3–6]. Vaginal progesterone has been shown to have higher uterine specificity than IM progesterone, with a higher endometrial concentration and lower serum concentration [7]. Numerous studies have compared the vaginal to IM route for luteal phase support

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(LPS) in IVF in terms of clinical outcomes. Most of these studies compared similar formulations of progesterone; however, doses of progesterone, study design, patient populations and outcome definitions varied.

For fresh cycles, the most recent meta-analysis included seven randomized controlled trials (RCTs) of various sizes comparing the vaginal to the IM route for LPS and revealed a summary OR of 1.24 (95% CI 1.03–1.50) for a combined outcome of either live birth (LB) or ongoing pregnancy, in favor of the vaginal route [2]. Other prospective studies and meta-analyses either reported neutral results [8–12], favored the vaginal route [13] or favored the IM route [14] for clinical pregnancy, ongoing pregnancy or LB. Miscarriage was not reported by all studies nor was the primary outcome studied. Among the prospective studies that reported on this outcome, there was no difference between the two routes of administration [8, 13, 15]. Retrospective studies report conflicting results [16–23].

For frozen ET cycles, there have been two recent RCTs comparing IM progesterone to vaginal progesterone, studying two slightly different populations. The most recent was a well-designed three-arm RCT comparing IM progesterone alone to vaginal progesterone alone to a combination of daily vaginal progesterone with IM progesterone every 3rd day [24]. Results revealed a statistically significantly higher miscarriage rate and lower LB rate in patients receiving only vaginal progesterone compared to the other two groups. The second RCT on 1447 patients revealed no difference in clinical outcome, including risk of miscarriage, between the two routes of administration [25]. Several retrospective studies and abstracts have been published with conflicting results [26–31]. In all studies published so far, both in fresh and frozen cycles, the type and route of progesterone used was consistent throughout the entire luteal cycle and early pregnancy.

Overall, vaginal progesterone seems as effective as IM progesterone for attaining a LB in fresh IVF cycles; however, in frozen ET cycles this may not be the case. In IVF practices however, old habits die hard, and in certain countries IM is still the default choice for progesterone [32]. Moreover, for the outcome of miscarriage, results are conflicting. Therefore, this study was performed to determine if beginning LPS with IM progesterone and then switching to vaginal progesterone once a positive pregnancy test is established yields a higher miscarriage risk than staying on IM progesterone.

Methods

Study design

A retrospective cohort study was performed in a single university-affiliated private fertility clinic in Montreal, Canada, comparing two regimens of LPS: (1) IM progesterone up until the positive pregnancy test, followed by a switch to vaginal (PV) progesterone until 10 weeks' gestation versus (2) IM progesterone during the entire luteal phase through to 10 weeks' gestation. It was the patients' choice whether to switch to vaginal or stay on IM progesterone.

The study population consisted of females aged 18–50 years with a positive pregnancy test after a stimulated fresh IVF cycle or substituted frozen ET performed between 2013 and 2016. Only autologous transfers and first IVF pregnancies were included. Biochemical pregnancies were excluded as they are often diagnosed at the time of the initial pregnancy test when beta-hCG levels are low or dropping, which also corresponds to the time of progesterone switch. Also excluded were pregnancies from oocyte donor or surrogacy cycles, and pregnancies from natural fresh IVF or natural frozen cycles as vaginal progesterone is generally used all throughout for LPS.

The main outcome measured was risk of miscarriage < 24 weeks gestation per non-biochemical pregnancy, and miscarriage was defined as per the European Society of Human Reproduction and Embryology (ESHRE) definition [33]. The secondary outcome measured was miscarriage risk ≤ 12 weeks per non-biochemical pregnancy. It was not possible to calculate implantation or LB risks as the dataset contained only patients with a positive pregnancy and biochemical pregnancies were excluded from this study.

Treatment protocols

In fresh IVF cycles, controlled ovarian stimulation protocols included GnRH antagonist, long GnRH agonist and short microdose flare. The choice of protocol and gonadotropin dosage was made by the treating physician and dosage modifications were made during cycle monitoring. Ovulation was triggered with hCG 5000 IU SC when ≥ 3 follicles reached 18 mm in diameter and oocyte retrieval was performed 36 h later. Fertilization was performed by intracytoplasmic sperm injection or standard IVF based on sperm parameters. Luteal phase support with IM progesterone 50 mg daily and transdermal 17ß estradiol (Climara, Bayer Inc.) 100 ug was started on the day of oocyte retrieval and either cleavage or blastocyst ET was performed in the following days. If pregnancy test was positive 15 days after oocyte retrieval, the patient could choose to stay on IM progesterone or switch to PV progesterone. Progesterone treatment was continued until 10 weeks' gestation and estrogen until 8 weeks' gestation.

For substituted frozen ET cycles, one dose of leuprolide-acetate 3.75 IM (Lupron-depot, AbbVIE Corp.) was given on day 20 of the preceding cycle. Endometrial preparation was initiated on day 3 of the cycle with transdermal estrogen (Cimara) 100ug and increased to 200 ug on day 7. IM

progesterone 50 mg daily was initiated when endometrial thickness generally reached 8 mm on ultrasound, and ET was performed on the 3rd, 4th or 6th day of progesterone for day 2, 3 or 5/6 embryos, respectively. The offer to switch to vaginal progesterone was done similarly to the fresh cycles and the duration of LPS was similar as well. In both fresh and frozen cycles, the indication to switch from IM to PV progesterone was based on patient preference.

Power calculation

A sample size of 1988 patients provides 84% power, at the 0.05 significance level, to detect a difference of 6% in miscarriage risk between staying on IM progesterone and switching to vaginal progesterone after a positive pregnancy test.

This calculation was based on results of an RCT interim analysis showing that pregnancy loss risks were 23% versus 11% when vaginal progesterone alone was compared to vaginal alternating with IM progesterone or IM progesterone alone [34]. The lower miscarriage proportion was increased to 17% for the power calculation in order to be conservative as 11% is very low, and this study reflects fresh and frozen ETs.

Statistical analyses

Continuous variables were recoded as categorical either for simplicity (duration of infertility, parity, previous miscarriages, prior failed ETs and number of good quality embryos from the fresh IVF cycle), by convention (BMI) or by levels of ovarian reserve (antral follicle count (AFC), antimullerian hormone (AMH), follicle stimulation hormone (FSH)), with the reference category for each being the lowest category.

Descriptive analyses were performed to assess baseline characteristics by exposure and outcome groups in turn, using two-sided *t* tests for continuous variables and Chi-squared tests for categorical variables. Logistic regression was used to evaluate the crude association between progesterone type and miscarriage as well as adjusted ORs for this association adjusted for each potential confounder in turn. Effect modification was assessed by comparing stratum specific ORs and their confidence intervals between each other as well as by a test of homogeneity for each variable. A multivariable logistic regression analysis was performed to assess the association between type of progesterone and miscarriage, controlling for BMI, prior failed ETs, prior miscarriages and type of ET (fresh vs frozen). A complete case analysis was performed, therefore missing values were dropped for all variables included in the final models. In all analyses, a p value < 0.05 was considered statistically significant.

All statistical analyses were carried out using STATA 13.1 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.).

Ethics

Access to patients' files was approved by the Quebec Commission of access to information (ref: 1014586-S). Ethics approval was obtained by University of Montreal Hospital Center Research Ethics Committee (CR-CHUM; ref: 15.387).

Results

Overall, there were 1988 patients with complete data on exposure and outcome and with a positive pregnancy test after ET between 2013 and 2016 that were included in the analysis. Of these women, 1221 stayed on IM progesterone and 767 women switched to PV progesterone after a positive pregnancy test. Table 1 presents the baseline characteristics of these women by exposure status. The majority of those who switched over to vaginal progesterone used Endometrin (Ferring Pharmaceuticals Inc.) 100 mg three times daily (744 women), 6 used Prometrium (Merck Canada Inc.) 300 mg twice daily, 12 used Crinone gel (EMD Serono Inc.) 8% once daily, and for 5 women this was not specified. Women who stayed on IM progesterone had more frequently experienced at least one prior miscarriage (25.9% vs 20.6%, $p = 0.005$) and at least one previously failed ET (46.8 vs 36.0%, $p < 0.001$) than women who switched to vaginal progesterone. There were more fresh than frozen ETs overall; and within exposure groups, the proportion of fresh transfers was higher in the vaginal compared to IM group (66.1% vs 60.4%, $p = 0.011$).

With regard to the primary outcome measure, 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 ($p = 0.37$) (Fig. 1). The mean gestational age at the time of miscarriage was similar between the groups (8.4 ± 2.2 weeks in IM group, 8.5 ± 3.3 weeks in PV groups; $p = 0.61$). There were only 12 patients in both groups who experienced a miscarriage between 12 and 24 weeks, and associations for those with miscarriage < 12 weeks were similar to results for miscarriage < 24 weeks. Significant associations ($p < 0.05$) were found between miscarriage and age at oocyte pickup, BMI, AMH, AFC, 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 0.73–1.13) for the association between progesterone type and miscarriage. Factors found to be associated with

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

	IM prog $N=1221$	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)	
Age at embryo transfer (mean ± SD)	34.5 (±4.5)	34.2 (±4.5)	0.072
BMI, kg/m^2 (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)	
FSH (mean ± SD)	6.1 (±2.3)	6.2 (±2.3)	0.917
< 10	1060 (86.8)	664 (86.6)	
≥ 10	63 (5.2)	36 (4.7)	0.669
Missing	98 (8.0)	67 (8.7)	
AMH (ng/ml) (mean ± SD)	3.36 (±3.4)	3.30 (±3.0)	0.729
< 1	195 (16.0)	127 (16.6)	
1–2.49	384 (31.5)	224 (29.2)	
2.5–4.99	338 (27.7)	228 (29.7)	0.667
≥ 5	229 (18.8)	143 (18.6)	
Missing	75 (6.1)	45 (5.9)	
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

Table 1 (continued)

	IM prog $N=1221$	PV prog $N=767$	p value*
Missing	3 (0.3)	0 (0.0)	
No. of good quality embryos produced in the original cycle (mean ± SD)	3.35 (2.1)	3.21 (1.9)	0.140
1–2 (n, %)	471 (38.6)	311 (40.6)	
≥ 3	749 (61.3)	455 (59.3)	0.376
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. of 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)	

For variables with no "missing" category, there are no missing values

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

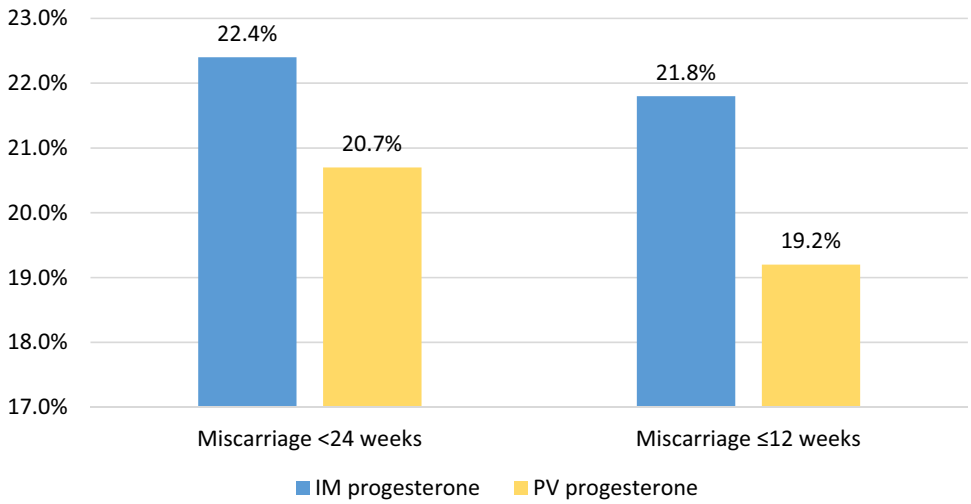

Fig. 1 Clinical outcomes by type of Progesterone. *IM* intramuscular, *PV* vaginal; p value 0.370 for miscarriage < 24 weeks and 0.161 for miscarriage < 12 weeks

both exposure and outcome were history of prior miscarriage, prior failed ETs and type of ET (fresh vs frozen). A test of homogeneity yielded a statistically significant result for AFC ($p=0.023$), showing a lower odds of miscarriage with vaginal progesterone in patients with a lower AFC.

Table 2 presents results of the multivariable logistic regression. A complete case analysis was performed; therefore, 6.5% of data (accounting for missing data) was dropped. This analysis yielded an aOR of 0.97 (95% CI 0.77–1.22, $p=0.778$) when controlling for BMI, prior failed ETs, prior miscarriages and type of ET (fresh vs frozen). Controlling for the interaction between type of progesterone and AFC showed that in the lower level of AFC, those on vaginal progesterone had 37% lower chance of miscarriage than those on IM progesterone (aOR 0.63, 95% CI 0.42–0.93).

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 2 Results of multivariable logistic regression models for the association between type of progesterone and miscarriage < 24 weeks ($N = 1858$)

	aOR (95% CI)	*p* value
IM progesterone	1.00	
Vaginal progesterone	0.97 (0.77–1.22)	0.778
By level of AFC (effect modification)		
AFC ≤ 13	0.63 (0.42–0.93)	0.020
AFC 14–24	1.13 (0.78–1.64)[a]	0.531
AFC ≥ 25	1.39 (0.90–2.16)[a]	0.139

aOR adjusted odds ratio, adjusted for BMI, prior miscarriage, prior failed ET and type of ET (fresh vs frozen)

[a]OR represents increase in odds from one category to the next

Discussion

The findings of this study suggest no association between type of progesterone supplementation and miscarriage after a positive pregnancy test following ET, and this even after adjusting for potential confounders. The association between staying on IM progesterone and a history of prior miscarriage and prior failed ETs can likely be explained by opting for a more "aggressive" form of progesterone with a history of negative outcome. An interesting finding is that once controlled for effect modification by level of AFC, a lower odds of miscarriage with vaginal compared to IM progesterone is revealed in women with a low AFC (aOR 0.63, 95% CI 0.42–0.93). The direction of this OR shifts in the higher AFC category. The same trend was found per strata of AMH and FSH; however, AMH was not included in the final model as AMH and AFC are collinear, and FSH is a less reliable marker of ovarian reserve [35]. A hypothesis for these findings may be that in women with lower ovarian reserve, the luteal phase is less negatively affected by a lower estradiol level during stimulation, and therefore requires less progesterone supplementation; however, this would only hold true for fresh cycles.

Miscarriage risks in this study are higher than those typically reported in the literature. This may be because most studies report miscarriage risk as a proportion of positive pregnancies, whereas in this study we reported miscarriage as a proportion of all non-biochemical pregnancies.

This is the first study to our knowledge evaluating the effect of switching from one type of progesterone to another during the same cycle. For this reason, as well as because pregnancy loss is studied as a proportion of non-biochemical pregnancies, head-to-head comparison with other studies is difficult. The majority of studies published on the matter did not perform a priori sample size or power calculations, and when present it was to detect a difference in pregnancy or LB rates. There seems to be consensus in the literature that for fresh ETs, there is no difference in LB risks between the two types of progesterone [2]. This may explain the finding in our study that there was a higher proportion of fresh transfers in the group of women who chose to switch to vaginal progesterone. Among all RCTs on fresh autologous cycles reporting on miscarriage, the difference between the two routes of progesterone also does not seem to differ [8, 12, 13, 15, 16, 19–22], except in two RCTs: one of which dates back to 1992 and includes techniques which are no longer relevant [10]; and another comparing vaginal progesterone to a synthetic IM progesterone rather than natural [14]. For frozen cycles, the evidence is less uniform in both retrospective studies and RCTs [12, 24, 25, 28, 29, 36, 37]. The most recent and well-designed RCT by Devine et al. (2021) shows that vaginal progesterone alone leads to higher miscarriage risk that the other two groups receiving IM progesterone alone or a combination of IM and vaginal progesterone (27% vs 19% vs 15%, respectively). In our study, results did not differ when the analysis was performed in fresh and frozen groups separately (aOR 0.83, 95% CI 0.62–1.12; aOR 1.26, 95% CI 0.86–1.83, respectively; data not shown), although our study was not powered for this analysis. Interestingly, the daily dosage of vaginal progesterone in the Devine study was higher than that used in our study, likely reinforcing that IM progesterone is crucial in the early period of LPS.

Strengths and limitations

The number of patients in this study is larger than that in most prior studies [3, 4, 6, 8–10, 13, 15, 17–24, 26–30, 37], even when considering that fresh and frozen cycles are published together in our study. Also, this study is adequately powered to detect a difference in miscarriage risks, whereas the prior retrospective and some of the prospective literature did not provide sample size calculations or study miscarriage as a primary outcome. In addition, many variables were considered, allowing to evaluate confounding and to clearly display the demographic distribution of this population, pertinent for external validity.

This study has several limitations, notably its retrospective design. Sources of bias with regard to data collection include: potential misclassification of type of progesterone exposure due to charting errors if these errors were related with outcome, as well as substantial missing data for certain variables, such as ovarian reserve markers. However, distribution of missing values was not different in exposure and outcome groups, and when variables were assessed sequentially in the multivariable model, the effect estimate did not change once data with missing values were dropped. Some potential confounders may not have been accounted for, such as preimplantation genetic testing (PGT), for which data were not available but which is known to affect miscarriage risk [38, 39]. The type of ovarian stimulation protocol from which the

embryos were derived was also not considered in the analysis; however, the type of protocol has not been shown to affect miscarriage risk in the majority of studies on this matter [40–44]. A stratified analysis by fresh and frozen ET lacked adequate power; however this would have been interesting as the effect of IM and vaginal progesterone in these two groups seems to differ in the literature. In this study, 63% of ETs were fresh, and this may have contributed to the null result.

Conclusions

The results of this study can reassure clinicians and patients that switching from IM progesterone to vaginal progesterone after a positive pregnancy test is unlikely to be detrimental with regard to miscarriage and may offer some new flexibility in treatment options. This corroborates with studies that show that effects of progesterone are most crucial during the 2 weeks between its initiation and the pregnancy test in fresh cycles [45, 46]. This has not yet been shown for frozen cycles; however the importance of progesterone in the early luteal phase seems apparent [24], and the results of our study support this.

Future research should be performed to corroborate results of this study, ideally as RCTs, and most interestingly if limited to frozen cycles. Although this study did not find an association in the frozen ET group specifically, this study was not powered to study this specifically.

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Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by TS, NZ, LL and SP. Data analysis was performed by TS. The first draft of the manuscript was written by TS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The authors confirm that the data supporting the findings of this study is available within the article. The final dataset used for the analysis in this study is available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval and consent Access to patients' files was approved by the Quebec Commission of access to information (ref: 1014586-S). Ethics approval was obtained by the University of Montreal Hospital Center Research Ethics Committee (CR-CHUM; ref: 15.387).

Consent to publish Not applicable.

References

1. Fatemi HM, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P (2007) An update of luteal phase support in stimulated IVF cycles. Hum Reprod Update 13(6):581–590. https://doi.org/10.1093/humupd/dmm021
2. van der Linden M, Buckingham K, Farquhar C, Kremer JAM (2015) Metwally M (2015) Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 7:CD009154
3. Beltsos AN, Sanchez MD, Doody KJ, Bush MR, Domar AD, Collins MG (2014) Patients' administration preferences: progesterone vaginal insert (Endometrin(R)) compared to intramuscular progesterone for Luteal phase support. Reprod Health 11:78. https://doi.org/10.1186/1742-4755-11-78
4. Propst AM, Hill JA, Ginsburg ES, Hurwitz S, Politch J, Yanushpolsky EH (2001) A randomized study comparing Crinone 8% and intramuscular progesterone supplementation in in vitro fertilization-embryo transfer cycles. Fertil Steril 76(6):1144–1149. https://doi.org/10.1016/s0015-0282(01)02872-2
5. Doody K, Bush M, Collins M (2012) Progesterone supplementation for luteal support: efficacy and patient experiences with vaginal inserts (Endometrin®) versus intramuscular injection. Fertil Steril 97(3):S18. https://doi.org/10.1016/j.fertnstert.2012.01.040
6. Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M (2010) Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective randomized study. Fertil Steril 94(7):2596–2599. https://doi.org/10.1016/j.fertnstert.2010.02.033
7. Cicinelli E, Schonauer LM, Galantino P, Matteo MG, Cassetta R, Pinto V (2000) Mechanisms of uterine specificity of vaginal progesterone. Hum Reprod 15(Suppl 1):159–165. https://doi.org/10.1093/humrep/15.suppl_1.159
8. Kahraman S, Karagozoglu SH, Karlikaya G (2010) The efficiency of progesterone vaginal gel versus intramuscular progesterone for luteal phase supplementation in gonadotropin-releasing hormone antagonist cycles: a prospective clinical trial. Fertil Steril 94(2):761–763. https://doi.org/10.1016/j.fertnstert.2009.10.004
9. Schoolcraft WB, Hesla JS, Gee MJ (2000) Experience with progesterone gel for luteal support in a highly successful IVF programme. Hum Reprod 15(6):1284–1288
10. Smitz J, Devroey P, Faguer B, Bourgain C, Camus M, Van Steirteghem AC (1992) A prospective randomized comparison of intramuscular or intravaginal natural progesterone as a luteal phase and early pregnancy supplement. Hum Reprod 7(2):168–175. https://doi.org/10.1093/oxfordjournals.humrep.a137611
11. Zarutskie PW, Phillips JA (2009) A meta-analysis of the route of administration of luteal phase support in assisted reproductive technology: vaginal versus intramuscular progesterone. Fertil Steril 92(1):163–169. https://doi.org/10.1016/j.fertnstert.2009.02.018
12. Abdelhakim AM, Abd-ElGawad M, Hussein RS, Abbas AM (2020) Vaginal versus intramuscular progesterone for luteal phase support in assisted reproductive techniques: a systematic review and meta-analysis of randomized controlled trials. Gynecol Endocrinol 36(5):389–397. https://doi.org/10.1080/09513590.2020.1727879
13. Silverberg KM, Vaughn TC, Hansard LJ, Burger NZ, Minter T (2012) Vaginal (Crinone 8%) gel vs. intramuscular progesterone in oil for luteal phase support in in vitro fertilization: a large prospective trial. Fertil Steril 97(2):344–348. https://doi.org/10.1016/j.fertnstert.2011.11.018
14. Unfer V, Casini ML, Costabile L, Gerli S, Baldini D, Di Renzo GC (2004) 17 alpha-hydroxyprogesterone caproate versus

intravaginal progesterone in IVF-embryo transfer cycles: a prospective randomized study. Reprod Biomed Online 9(1):17–21
15. Dal Prato L, Bianchi L, Cattoli M, Tarozzi N, Flamigni C, Borini A (2008) Vaginal gel versus intramuscular progesterone for luteal phase supplementation: a prospective randomized trial. Reprod Biomed Online 16(3):361–367
16. Chi HB, Liu NN, Li R, Tao LY, Chen LX, Qiao J (2018) Comparison of vaginal gel and intramuscular progesterone for in vitro fertilization and embryo transfer with gonadotropin-releasing hormone antagonist protocol. Chin Med J (Engl) 131(13):1557–1561. https://doi.org/10.4103/0366-6999.235106
17. Damario MA, Goudas VT, Session DR, Hammitt DG, Dumesic DA (1999) Crinone 8% vaginal progesterone gel results in lower embryonic implantation efficiency after in vitro fertilization-embryo transfer. Fertil Steril 72(5):830–836. https://doi.org/10.1016/s0015-0282(99)00364-7
18. Ho CH, Chen SU, Peng FS, Chang CY, Yang YS (2008) Luteal support for IVF/ICSI cycles with Crinone 8% (90 mg) twice daily results in higher pregnancy rates than with intramuscular progesterone. J Chin Med Assoc 71(8):386–391. https://doi.org/10.1016/s1726-4901(08)70088-1
19. Jabara S, Barnhart K, Schertz JC, Patrizio P (2009) Luteal phase bleeding after IVF cycles: comparison between progesterone vaginal gel and intramuscular progesterone and correlation with pregnancy outcomes. J Exp Clin Assist Reprod 6:6
20. Khan N, Richter KS, Newsome TL, Blake EJ, Yankov VI (2009) Matched-samples comparison of intramuscular versus vaginal progesterone for luteal phase support after in vitro fertilization and embryo transfer. Fertil Steril 91(6):2445–2450. https://doi.org/10.1016/j.fertnstert.2008.03.072
21. Mitwally MF, Diamond MP, Abuzeid M (2010) Vaginal micronized progesterone versus intramuscular progesterone for luteal support in women undergoing in vitro fertilization-embryo transfer. Fertil Steril 93(2):554–569. https://doi.org/10.1016/j.fertnstert.2009.02.047
22. Papaleo E, Quaranta L, Molgora M (2010) Intramuscular vs intravaginal natural progesterone in patients undergoing in vitro fertilization-embryo transfer cycles. A retrospective observational, case-control study. Eur Rev Med Pharmacol Sci 14(2):103–106
23. Satir F, Toptas T, Inel M, Erman-Akar M, Taskin O (2013) Comparison of intravaginal progesterone gel and intramuscular 17-alpha-hydroxyprogesterone caproate in luteal phase support. Exp Ther Med 5(6):1740–1744. https://doi.org/10.3892/etm.2013.1049
24. Devine K, Richter KS, Jahandideh S, Widra EA, McKeeby JL (2021) Intramuscular progesterone optimizes live birth from programmed frozen embryo transfer: a randomized clinical trial. Fertil Steril 116(3):633–643. https://doi.org/10.1016/j.fertnstert.2021.04.013
25. Wang Y, He Y, Zhao X, Ji X, Hong Y, Wang Y, Zhu Q, Xu B, Sun Y (2015) Crinone gel for luteal phase support in frozen-thawed embryo transfer cycles: a prospective randomized clinical trial in the Chinese population. PLoS ONE 10(7):e0133027. https://doi.org/10.1371/journal.pone.0133027
26. Haddad G, Saguan DA, Maxwell R, Thomas MA (2007) Intramuscular route of progesterone administration increases pregnancy rates during non-downregulated frozen embryo transfer cycles. J Assist Reprod Genet 24(10):467–470. https://doi.org/10.1007/s10815-007-9168-z
27. Kaser DJ, Ginsburg ES, Missmer SA, Correia KF, Racowsky C (2012) Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer. Fertil Steril 98(6):1464–1469. https://doi.org/10.1016/j.fertnstert.2012.08.007
28. Mathur N, Uhler ML, Feinberg EC (2013) Comparison of luteal phase support regimens in frozen embryo transfer (FET) cycles from comprehensive chromosome screening. Fertil Steril 1:S298
29. Carr BR, Doody KJ (2009) Comparison of endometrin and intramuscular progesterone for frozen-thawed embryo transfer. Fertil Steril 1:S244
30. Shapiro DB, Pappadakis JA, Ellsworth NM, Hait HI, Nagy ZP (2014) Progesterone replacement with vaginal gel versus i.m. injection: cycle and pregnancy outcomes in IVF patients receiving vitrified blastocysts. Hum Reprod 29(8):1706–1711. https://doi.org/10.1093/humrep/deu121
31. Bakkensen JB, Racowsky C, Thomas AM, Lanes A, Hornstein MD (2020) Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support following blastocyst cryopreserved single embryo transfer: a retrospective cohort study. Fertil Res Pract 6:10. https://doi.org/10.1186/s40738-020-00079-y
32. Casper RF (2014) Luteal phase support for frozen embryo transfer cycles: intramuscular or vaginal progesterone? Fertil Steril 101(3):627–628. https://doi.org/10.1016/j.fertnstert.2014.01.018
33. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S, Vermeulen N, Goddijn M (2018) ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open 2:004. https://doi.org/10.1093/hropen/hoy004
34. Devine K, Richter KS, Widra EA, McKeeby JL (2018) Vitrified blastocyst transfer cycles with the use of only vaginal progesterone replacement with Endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled noninferiority trial. Fertil Steril 109(2):266–275. https://doi.org/10.1016/j.fertnstert.2017.11.004
35. Tal R, Seifer DB (2017) Ovarian reserve testing: a user's guide. Am J Obstet Gynecol 217(2):129–140. https://doi.org/10.1016/j.ajog.2017.02.027
36. Wambach C, Ambartsumyan G, Surrey M, Hill D, Danzer H (2011) Mode of luteal phase progesterone support after frozen embryo transfer does not affect live birth rates. Fertil Steril 1:S26
37. Lightman A, Kol S, Itskovitz-Eldor J (1999) A prospective randomized study comparing intramuscular with intravaginal natural progesterone in programmed thaw cycles. Hum Reprod 14(10):2596–2599. https://doi.org/10.1093/humrep/14.10.2596
38. Schoolcraft WB, Katz-Jaffe MG (2013) Comprehensive chromosome screening of trophectoderm with vitrification facilitates elective single-embryo transfer for infertile women with advanced maternal age. Fertil Steril 100(3):615–619. https://doi.org/10.1016/j.fertnstert.2013.07.1972
39. Grifo JA, Hodes-Wertz B, Lee HL, Amperloquio E, Clarke-Williams M, Adler A (2013) Single thawed euploid embryo transfer improves IVF pregnancy, miscarriage, and multiple gestation outcomes and has similar implantation rates as egg donation. J Assist Reprod Genet 30(2):259–264. https://doi.org/10.1007/s10815-012-9929-1
40. Yang R, Guan Y, Perrot V, Ma J, Li R (2021) Comparison of the long-acting GnRH agonist follicular protocol with the GnRH antagonist protocol in women undergoing in vitro fertilization: a systematic review and meta-analysis. Adv Ther 38(5):2027–2037. https://doi.org/10.1007/s12325-020-01612-7
41. Yang AM, Xu X, Han Y, Wei JJ, Hao GM, Cui N, Zhao ZM, Wang W, Huang X (2021) Risk factors for different types of pregnancy losses: analysis of 15,210 pregnancies after embryo transfer. Front Endocrinol (Lausanne) 12:683236. https://doi.org/10.3389/fendo.2021.683236
42. Li R, Guan Y, Yang R, Perrot V, Juan MA (2020) Comparison of controlled ovary stimulation protocols for in vitro fertilisation: a meta-analysis. Fertil Steril 114(3):e442–e444. https://doi.org/10.1016/j.fertnstert.2020.08.1282
43. Kadoura S, Alhalabi M, Nattouf AH (2022) Conventional GnRH antagonist protocols versus long GnRH agonist protocol in IVF/

ICSI cycles of polycystic ovary syndrome women: a systematic review and meta-analysis. Sci Rep 12(1):4456. https://doi.org/10.1038/s41598-022-08400-z

44. Hu L, Du J, Lv H, Zhao J, Chen M, Wang Y, Wu F, Liu F, Chen X, Zhang J, Ma H, Jin G, Shen H, Chen L, Ling X, Hu Z (2018) Influencing factors of pregnancy loss and survival probability of clinical pregnancies conceived through assisted reproductive technology. Reprod Biol Endocrinol 16(1):74. https://doi.org/10.1186/s12958-018-0390-6
45. Kyrou D, Fatemi HM, Zepiridis L, Riva A, Papanikolaou EG, Tarlatzis BC, Devroey P (2011) Does cessation of progesterone supplementation during early pregnancy in patients treated with recFSH/GnRH antagonist affect ongoing pregnancy rates? A randomized controlled trial. Hum Reprod 26(5):1020–1024. https://doi.org/10.1093/humrep/der012
46. Pan SP, Chao KH, Huang CC, Wu MY, Chen MJ, Chang CH, Yang JH, Yang YS, Chen SU (2018) Early stop of progesterone supplementation after confirmation of pregnancy in IVF/ICSI fresh embryo transfer cycles of poor responders does not affect pregnancy outcome. PLoS ONE 13(8):e0201824. https://doi.org/10.1371/journal.pone.0201824