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Evaluation of two luteal support regimens, intramuscular progesterone and progesterone vaginal gel, for vitrified-warmed embryo transfer in women with chronic salpingitis: a single-center 8-year retrospective study

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Abstract

Background Chronic salpingitis is one of the most common causes of female infertility. Luteal support is a critical step for embryo transfer. Here, we evaluated the effects of two luteal support regimens, intramuscular progesterone (IMP) and progesterone vaginal gel (VAG), on the pregnancy outcomes in patients with chronic salpingitis undergoing vitrified-warmed embryo transfer.

Methods This study retrospectively analyzed 2240 patients with chronic salpingitis undergoing vitrified-warmed embryo transfer from 2015 to 2022 at our center. Patients were categorized into IMP group ($n=1039$) and VAG group ($n=1201$). Inverse probability of treatment weighting (IPTW) was used to balance baseline characteristics. Univariate and multivariate logistic regression models were conducted to analyze pregnancy outcomes.

Results After IPTW, baseline demographic characteristics were balanced and outcome indicators were comparable. Crude analysis showed a higher live birth rate (OR 1.25, 95% CI 1.017–1.537, $p=0.034$) and ongoing pregnancy rate (OR 1.231, 95% CI 1.002–1.512, $p=0.047$) as well as lower miscarriage rate (OR 0.612, 95% CI 0.461–0.812, $p<0.001$) in IMP group compared with VAG group. After adjusting for confounders, IMP group still presented a higher live birth rate (OR 1.256, 95% CI 1.019–1.547, $p=0.033$), ongoing pregnancy rate (OR 1.236, 95% CI 1.004–1.521, $p=0.046$) and lower miscarriage rate (OR 0.588, 95% CI 0.443–0.782, $p<0.001$). No statistical differences were observed in biochemical pregnancy rate, clinical pregnancy rate, twin pregnancy rate, preterm delivery rate, and full-term delivery rate before and after adjustment.

Conclusions For infertile patients with chronic salpingitis undergoing vitrified-warmed embryo transfer, IMP presents greater advantages. VAG may be not recommended as an alternative for luteal support in such patients. These findings, based on our 8-year-long retrospective experience, may contribute to a better selection of luteal support protocol for infertile patients with tubal factors.

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Keywords Chronic salpingitis, Vitrified-warmed embryo transfer, Intramuscular progesterone, Inverse probability of treatment weighting, Luteal support, Pregnancy outcomes, Progesterone vaginal gel

Introduction

Infertility is a major global health issue, significantly affecting the physical and mental health of couples at childbearing ages. For women, infertility is mainly caused by ovarian, cervical, uterine, and tubal factors. [1]. Among them, tubal infertility due to tubal obstruction or pelvic adhesions is the leading cause of female infertility, accounting for approximately 11% to 67% [1, 2]. Miscarriage, premature birth, low birth weight delivery and ectopic pregnancy are all related with tubal factor infertility and pelvic adhesion [3, 4]. Pelvic inflammatory disease (PID) is the most common infectious process causing tubal infertility [5]. PID-induced tubal injury can cause inflammation and persistent tubal alterations, including hydrosalpinx, tubal obstruction and fimbrial phimosis, eventually evolving into chronic salpingitis [1].

The widespread use of assisted reproductive technologies (ART) has helped infertile patients with chronic salpingitis meet their reproductive needs. Over the past four decades, in vitro fertilization (IVF) technology was broadly applied, and subsequent improvements in embryo cryopreservation techniques (vitrification) allowed for the long-term preservation of surplus embryos for further use. Compared with conventional fresh embryo transfer, frozen embryo transfer (FET) significantly improves the clinical pregnancy rate of each transfer [6], reduces the risk of ovarian hyperstimulation syndrome (OHSS) [7], and provides sufficient time for endometrial receptivity regulation [8–10].

Progesterone is essential for embryo implantation and pregnancy maintenance, by regulating endometrial growth and stability [11]. Disorders such as recurrent implantation failure (RIF) [12, 13] and recurrent pregnancy loss (RPL) [14, 15] have been shown to be associated with progesterone deficiency. The hormone replacement therapy (HRT) cycle is now the most used endometrial preparation protocol in FET, during which a certain dose of exogenous supplementation is required right after transplantation, with estrogen supplementation being the first step, followed by the crucial progesterone support [16]. A rational luteal support approach can fully improve the endometrial condition, early embryonic development, and live birth rate of ART. The main options for luteal support are human chorionic gonadotropin (HCG) supplementation and progesterone supplementation [17]. HCG is associated with a higher incidence of OHSS, [18, 19] making progesterone the preferred choice. At present, the main delivery methods of luteal support include: oral, intramuscular and transvaginal [20]. Oral progesterone is not recommended due to significant hepatic first-pass effects and adverse effects, such as drowsiness and dizziness [21]. Intramuscular progesterone (IMP) is stable and long-acting as the primary method of luteal support, but can cause skin-related adverse reactions at the injection site [22]. Progesterone vaginal gel (VAG) has become a favored alternative due to its simplicity, rapid absorption, and minimal systemic side effects [23]. However, it is affected by the uterine first-pass effects [24] and is associated with adverse symptoms related to vaginal irritation [25]. Previous studies showed similar pregnancy outcomes with IMP and VAG during FET cycles [26–28], but little research focused on specific infertility factors.

Tubal factor infertility, including chronic salpingitis, is a major concern in female infertility. For such patients, it is vitally important to explore the most appropriate luteal support regimen to achieve the best clinical outcomes. Therefore, we analyzed the pregnancy outcomes in chronic salpingitis patients with IMP and VAG luteal support protocols for vitrified-warmed embryo transfer at our center over the past 8 years. This study is the first to focus precisely on tubal factors and the results of our 8-year-long retrospective experience may help clinicians select optimal luteal support regimens for patients with tubal factor infertility in vitrified-warmed embryo transfer cycles.

Methods

Data gathering and study participants

This retrospective observational study was conducted at the Xuzhou Maternity and Child Health Care Hospital and the cases were admitted from January 2015 to December 2022. A total of 2240 vitrified-warmed embryo transfer cycles were eligible for inclusion in this study. The inclusion criteria were: (1) patients undergoing vitrified-warmed embryo transfer for the first time; (2) patients who are treated with HRT cycle for endometrial preparation; (3) patients with IMP or VAG for luteal support; (4) infertility caused by chronic salpingitis with or without persistent tubal alterations, such as tubal obstruction, hydrosalpinx and pelvic adhesion; and (5) women with at least one high quality transferable frozen embryo, referring to cleavage-stage embryos with grade I–II and 7–12 cells at day 3 (D3), and blastocyst-stage embryos with grade 4AA,

4AB, 4BA or 4BB at day 5 (D5) [29]. The exclusion criteria were: (1) maternal age ≥ 40 years; (2) women's BMI < 18 or > 28 kg/m^2 [27]; (3) uterus factors, such as uterine myoma, endometriosis, adenomyosis, or uterine malformations; (4) chromosomal abnormalities in either party; (5) women suffering from acute or chronic systemic disorders; (6) endometrial thickness < 8 mm before starting progesterone therapy; and (7) serum progesterone ≥ 1.5 ng/mL before starting progesterone therapy [27]. Figure 1 illustrates the overall design of this study.

The study was approved by the Ethics Committee of Xuzhou Maternity and Child Health Care Hospital on 31 October 2023 and was guided by the principles of the Helsinki Declaration.

Diagnosis and management of chronic salpingitis

Typically, infertile patients with chronic salpingitis who came to our center for vitrified-warmed embryo transfer experienced abdominal pain and increased vaginal discharge as their main symptoms. The fallopian tubes were usually thickened on one or both sides of the uterus with mild tenderness. If accompanied by hydrosalpinx, cystic mass could be palpated with limited mobility. For these patients, we mainly diagnosed by abdominal ultrasound and hysterosalpingography (HSG). The main changes

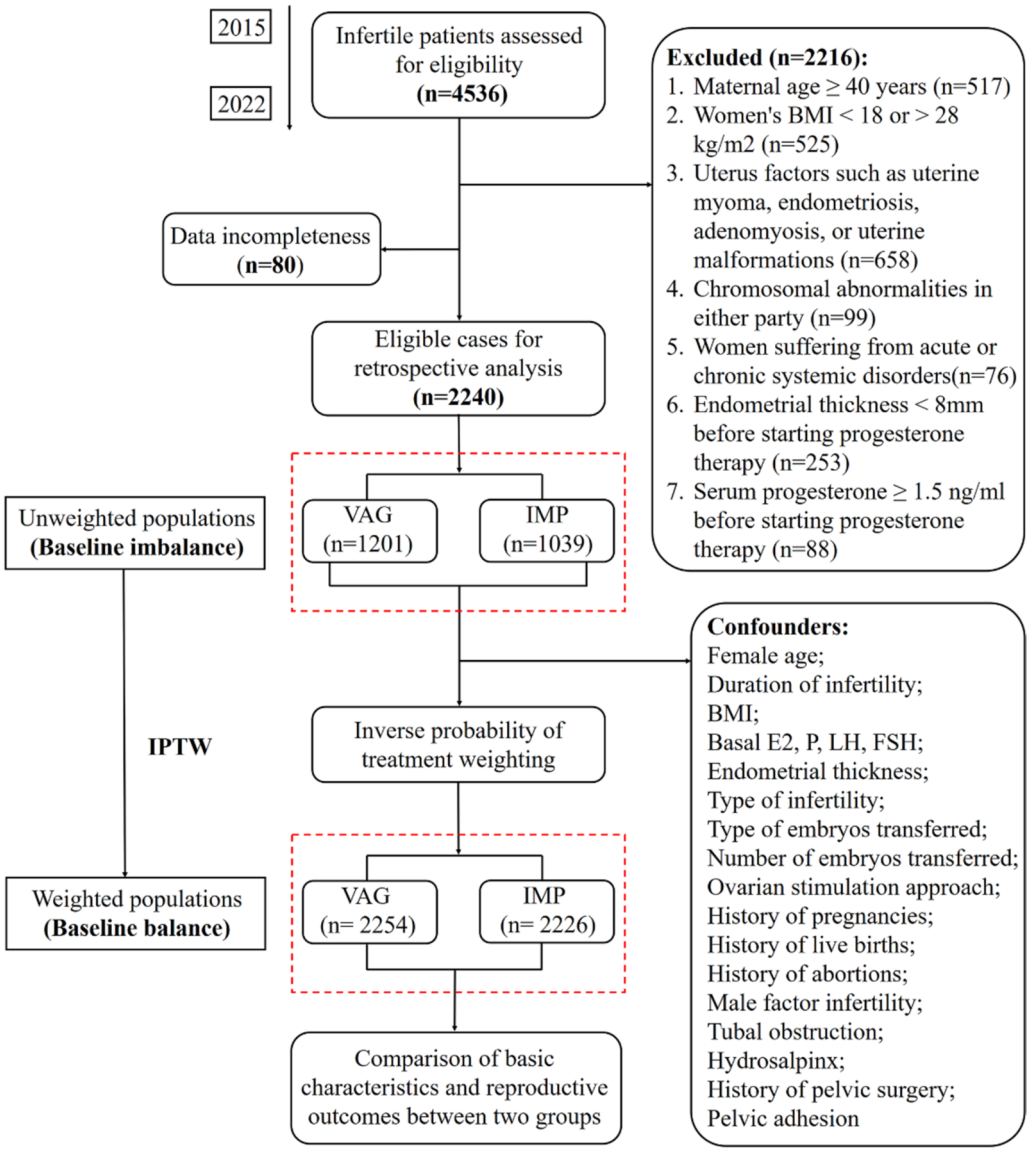

Fig. 1 Overall flow chart of this retrospective study

included tubal thickening, tubal obstruction, and the accumulation of serosity exudation leading to hydrosalpinx. Severe cases showed extensive adhesion, hyperplasia, and scar formation in pelvic tissues. For some cases, we also used invasive laparoscopy to further clarify the diagnosis. If patients were diagnosed with chronic salpingitis, a course of antibiotics would be prescribed. If pathogenetic condition recurred, surgical treatment, mainly salpingectomy, would be performed after evaluation. We have presented patients who have undergone pelvic surgery and those with a combination of tubal obstruction, hydrosalpinx, and pelvic adhesions in the baseline table. We treated these factors as confounders for subsequent analysis to minimize the impact of them on the final pregnancy outcomes.

Ovarian stimulation

The patients included in this study were treated with the following three main ovarian stimulation protocols: (1) long gonadotropin-releasing hormone agonist (GnRH-a) protocol. On the second day of the menstrual cycle, long-acting GnRH-a (Triptorelin Acetate for Injection, Ipsen Pharma Biotech, France) was administered at 3.75 mg/d. Vaginal B-ultrasound was performed to monitor the diameters of sinus follicles on the 28th day after the injection, and serum levels of estradiol (E2), luteinizing hormone (LH), and progesterone (P) were measured as well. Gonadotropin stimulation was initiated with human menopausal gonadotropin (HMG, Livzon, China) or recombinant human follicle stimulating hormone (Gonal-F, Merck, Switzerland) according to the actual situation of the patient. (2) Gonadotropin-releasing hormone antagonist (GnRH-ant) protocol. Starting from the second day of the menstrual cycle, 150–300 IU HMG (Livzon, China) or rhFSH (Merck, US) was given daily to promote ovulation. When the diameter of more than one dominant follicle was greater than 14 mm or the levels of LH exceeded 10 IU/L, GnRH-ant (Cetrorelix Acetate Powder for Injection, Merck, Switzerland) was introduced at 0.25 mg/d until HCG trigger day. (3) Mild stimulation protocol. Clomiphene citrate (CC, Hengshan Pharmaceutical Co., China) was administered orally at 100 mg/d starting on the second day of the patient's menstrual cycle. 150 IU HMG (Livzon, China) or rhFSH (Merck, US) was added intramuscularly on the fifth day of menstruation until HCG trigger day.

Embryo cryopreservation and warming

Vitrifying and preservation of embryos accorded to the conventional vitrification embryo freezing methods. Blastocysts and embryos were transferred to basic solution (BS) for 2 min at room temperature, then to equilibration solution (ES) for 8 min. After restoring to their original volume sizes, the embryos were then transferred to vitrification solution (VS) for 1 min, to frozen carriers within 30 s, and finally to liquid nitrogen for preservation. At the time of warming, blastocysts and embryos were removed from liquid nitrogen, immersed in thawing solution (TS) for 3 min, then transferred to dilution solution (DS) for 3 min and washing solution (WS) for 5 min, and finally transferred to blastocyst culture medium. The frozen embryos of in vitro culture in this study were all from day 3 (D3) or day 5 (D5).

Endometrial preparation and luteal support

Hormone replacement cycle (HRC) is currently the most commonly used method for endometrial preparation in women undergoing FET. Considering the large dataset of HRC cases at our center and the purpose to compare different methods of progesterone administration, we selected patients who accepted HRC for endometrial preparation as the research subjects to minimize potential confounding factors and enable a more accurate comparison within a homogeneous patient population. For those who met hormone levels and vaginal ultrasound standards, 6 mg/d E2 (Abbott Biologicals B.V., the Netherlands) was orally started on the second day of their menstrual cycles and continued for at least 7 days. Dosage adjustment was based on serum E2 levels and endometrial thickness. When the endometrial thickness was $\geq$ 8 mm, the serum E2 level reached 150 pg/mL and the serum progesterone level was not higher than 1.5 ng/mL, luteal support for endometrial transformation was provided with Crinone vaginal progesterone gel 8% (VAG, Merck, Germany) 90 mg/d or intramuscular progesterone (IMP, Kocak Farma, Turkey) 60 mg/d, respectively. Embryos were transferred 3 days after endometrial transformation in cleavage-stage embryos and 5 days after endometrial transformation in blastocyst-stage embryos [30]. The original hormone replacement and luteal support treatment was continued after transfer until 9–11 weeks of pregnancy. A total of 1039 cycles were included in the IMP group, and a total of 1201 cycles were included in the VAG group.

Indicators of pregnancy outcome

The primary outcome indicator in this study was the live birth rate, which was defined as the ratio of live birth cycles to all cycles. The secondary pregnancy outcome measures were biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, twin pregnancy rate, miscarriage rate, preterm delivery rate, and full-term delivery rate. The definition of biochemical pregnancy was that β-hCG exceeds 20 IU/l 14 days after embryo transfer. When one or multiple gestational sacs with fetal heartbeats were detected in the uterine cavity

by ultrasound at 4 weeks, we call it clinical pregnancy. Ongoing pregnancy referred to pregnancy beyond 12 pregnant weeks. Pregnancy with two fetuses in the uterine cavity at the same time was called twin pregnancy. Miscarriage was characterized as the termination of pregnancy before 28 gestational weeks per cycles. Delivery exceeding 28 pregnant weeks but less than 37 pregnant weeks was called preterm delivery. Birth occurring between 37 pregnant weeks and 42 pregnant weeks was considered as full-term delivery.

Statistical analysis

The statistical analysis of this study was completed by R version 4.3.1 (R Project for Statistical Computing, Austria). Continuous variables were presented as mean (standard deviation, SD) and categorical data were shown as frequency (proportion). To adjust the baseline balance, we generated a propensity model using inverse probability of treatment weighting (IPTW) [31]. The inverse probability of being in different groups gave each individual a weight as the predicted probability for each group, thus balancing the differences in baseline characteristics between two groups. Standardized mean differences (SMD) was used to assess the balance of baseline characteristics between groups, with SMD less than 0.1 considered to be balanced [30]. A univariate logistic regression model was used to analyze the differences in pregnancy outcomes between the IMP and VAG groups. Considering the interference of numerous confounders, we further used a multivariate logistic regression model to adjust for relevant confounding factors. The results of both models were presented as odds ratio (OR) (95% confidence intervals, 95% CI). A two-sided p value < 0.05 was considered statistically significant. The IPTW processing was conducted via the "RISCA" R package. "Tableone" R package was used to evaluate baseline characteristics and calculate SMD and p value. "Survey" R package was used to extract the weighted results for univariate and multivariate logistic regression analyses [29]. "Questionr" R package was used to calculate OR value. Relevant R scripts can be provided if required.

Results

Baseline characteristics of participants

Among 2240 women with chronic salpingitis who were eligible for this study, 1201 were treated with VAG and 1039 were treated with IMP for luteal support. The unweighted basic characteristics of patients are shown in Table 1. Before IPTW, there was a significant difference between the baseline conditions of two groups. Patients in the IMP group had longer infertility years ($p < 0.001$, SMD = 0.154), lower basal E2 levels ($p = 0.013$, SMD = 0.104), higher basal P levels ($p < 0.001$, SMD = 0.184), higher basal LH levels ($p = 0.017$, SMD = 0.099), and thinner endometrial thickness ($p < 0.001$, SMD = 0.152) compared with women in the VAG group. Moreover, there were significant differences in the type of embryos transferred ($p < 0.001$, SMD = 0.624) and number of embryos transferred ($p < 0.001$, SMD = 0.814). We also fully considered the impact of different ovarian stimulation approaches and the presence or absence of male factor infertility, tubal obstruction, hydrosalpinx, history of pelvic surgery, pelvic adhesion, history of pregnancies, history of live births and history of abortions on outcomes. Analysis results showed that there were significant differences in ovarian stimulation approaches ($p < 0.001$, SMD = 0.977) between two groups, as well as in the presence of male factor infertility ($p = 0.021$, SMD = 0.099), tubal obstruction ($p < 0.001$, SMD = 0.167), and history of live births ($p = 0.024$, SMD = 0.097). After IPTW, the baseline characteristics of two groups reached a balance, as shown in Table 2. No significant differences were observed in any of baseline characteristics ($p \geq 0.05$ and SMD < 0.1 for all) between two groups. The SMD values of baseline characteristics for two groups before and after IPTW weighting are shown in Fig. 2.

Pregnancy outcomes

With baseline balance, a rough analysis using a univariate logistic regression model revealed statistically comparable differences between IMP and VAG group, as shown in Table 3. The live birth rate of the IMP group was significantly higher than that of the VAG group (OR 1.25, 95% CI 1.017–1.537, $p = 0.034$). In the secondary pregnancy outcome indicators, there was a statistically significant difference in ongoing pregnancy rate and miscarriage rate between two groups: the IMP group had a higher ongoing pregnancy rate (OR 1.231, 95% CI 1.002–1.512, $p = 0.047$) and a lower miscarriage rate (OR 0.612, 95% CI 0.461–0.812, $p < 0.001$). No significant difference was observed in terms of biochemical pregnancy rate (OR 0.923, 95% CI 0.749–1.136 $p = 0.448$), clinical pregnancy rate (OR 0.943, 95% CI 0.769–1.157, $p = 0.576$), twin pregnancy rate (OR 1.055, 95% CI 0.758–1.47, $p = 0.75$), preterm delivery rate (OR 0.788, 95% CI 0.493–1.258, $p = 0.317$) and full-term delivery rate (OR 1.266, 95% CI 0.795–2.015, $p = 0.319$) between two groups.

Considering the presence of confounding factors, we further used a multivariate logistic regression model for analysis. As Table 3 shows, the live birth rate (OR 1.256, 95% CI 1.019–1.547, $p = 0.033$) and ongoing pregnancy rate (OR 1.236, 95% CI 1.004–1.521, $p = 0.046$) of the IMP group were still higher than that of the VAG group. Similarly, the miscarriage rate remained lower in the IMP group (OR 0.588, 95% CI 0.443–0.782, $p < 0.001$).

Table 1 Basic characteristics of unweighted populations for each luteal support group

Characteristics	Unmatched study populations			
	Progesterone vaginal gel ($n=1201$)	Intramuscular progesterone ($n=1039$)	*p*	SMD
Female age (years)	31.36 (4.08)	31.16 (4.25)	0.26	0.048
Duration of infertility (years)	3.75 (3.09)	4.23 (3.17)	< 0.001	0.154
Body mass index (kg/m^2)	22.55 (2.40)	22.64 (2.39)	0.382	0.037
Basal E2 (pg/mL)	37.40 (18.94)	35.24 (22.30)	0.013	0.104
Basal P (ng/mL)	0.43 (0.25)	0.48 (0.27)	< 0.001	0.184
Basal LH (mIU/mL)	5.92 (5.43)	6.80 (11.38)	0.017	0.099
Basal FSH (mIU/mL)	6.86 (2.35)	6.92 (2.41)	0.58	0.023
Endometrial thickness(mm)	9.40 (1.08)	9.24 (1.03)	< 0.001	0.152
Type of infertility			1	0.001
Primary infertility	462 (38.5)	400 (38.5)		
Secondary infertility	739 (61.5)	639 (61.5)		
Type of embryos transferred			< 0.001	0.624
Cleavage-stage embryos	540 (45.0)	771 (74.2)		
Blastocysts	661 (55.0)	268 (25.8)		
Number of embryos transferred			< 0.001	0.814
1	932 (77.6)	421 (40.5)		
2	269 (22.4)	618 (59.5)		
Ovarian stimulation approach			< 0.001	0.977
GnRH-a protocol	189 (15.7)	466 (44.9)		
GnRH-ant protocol	764 (63.6)	222 (21.4)		
Mild stimulation protocol	212 (17.7)	319 (30.7)		
Other protocols	36 (3.0)	32 (3.1)		
History of pregnancies	821 (68.4)	730 (70.3)	0.354	0.041
History of live births	394 (32.8)	389 (37.4)	0.024	0.097
History of abortions	416 (34.6)	402 (38.7)	0.052	0.084
Male factor infertility	395 (32.9)	391 (37.6)	0.021	0.099
Tubal obstruction	46 (3.8)	80 (7.7)	< 0.001	0.167
Hydrosalpinx	12 (1.0)	8 (0.8)	0.726	0.024
History of pelvic surgery	145 (12.1)	147 (14.1)	0.164	0.062
Pelvic adhesion	31 (2.6)	33 (3.2)	0.474	0.036

Continuous variables are presented as mean (SD) and categorical data are shown as n (%). $p \geq 0.05$ and SMD < 0.1 are regarded as achieving balance. When unweighted, it is evident that some of the parameters are not in balance

Furthermore, the other secondary reproductive outcomes were all consistent with the previous results and showed no differences.

Discussion

The aim of this 8-year retrospective study was to analyze the effects of two luteal support modalities on pregnancy outcomes in vitrified-warmed embryo transfer patients with chronic salpingitis. We observed that for patients who underwent vitrified-warmed embryo transfer and suffered from chronic salpingitis, 60 mg/d intramuscular progesterone for luteal support may be a better choice after endometrial preparation. The advantages were mainly in terms of higher live birth rate and ongoing pregnancy rate as well as lower miscarriage rate.

Comparison of the IMP and VAG regimens for endometrial preparation has been previously reported. A prospective study showed that patients treated with VAG had higher pregnancy and delivery rates than those treated with IMP [22]. In FET cycles, Jiang et al. [32] also found that compared with the IMP group, the VAG group had higher implantation rate, delivery rate, and live birth rate. In addition, the dosage of vaginal progesterone administration was associated with pregnancy outcomes: compared to the 900 mg/d VAG group, higher clinical pregnancy rate and live birth rate

Table 2 Basic characteristics of weighted populations for each luteal support group

Characteristics	Weighted (IPTW) study populations			
	Progesterone vaginal gel (*n* = 2254)	Intramuscular progesterone (*n* = 2226)	*p*	SMD
Female age (years)	31.23 (4.22)	31.31 (4.15)	0.705	0.02
Duration of infertility (years)	4.07 (3.23)	4.04 (3.08)	0.885	0.007
Body mass index (kg/m^2)	22.61 (2.42)	22.61 (2.38)	0.948	0.003
Basal E2 (pg/mL)	36.56 (17.91)	36.79 (27.92)	0.872	0.01
Basal P (ng/mL)	0.44 (0.26)	0.43 (0.26)	0.466	0.037
Basal LH (mIU/mL)	6.15 (7.50)	6.31 (8.86)	0.693	0.019
Basal FSH (mIU/mL)	6.89 (2.49)	6.90 (2.33)	0.959	0.003
Endometrial thickness (mm)	9.32 (1.06)	9.34 (1.12)	0.713	0.02
Type of infertility			0.891	0.007
Primary infertility	890 (39.5)	887 (39.8)		
Secondary infertility	1364 (60.5)	1339 (60.2)		
Type of embryos transferred			0.728	0.018
Cleavage-stage embryos	1331 (59.1)	1335 (60.0)		
Blastocysts	923 (40.9)	891 (40.0)		
Number of embryos transferred			0.967	0.002
1	1334 (59.2)	1319 (59.3)		
2	921 (40.8)	907 (40.7)		
Ovarian stimulation approach			0.961	0.026
GnRH-a protocol	692 (30.7)	662 (29.7)		
GnRH-ant protocol	987 (43.8)	976 (43.8)		
Mild stimulation protocol	511 (22.7)	525 (23.6)		
Other protocols	64 (2.9)	63 (2.8)		
History of pregnancies	1549 (68.7)	1523 (68.4)	0.903	0.006
History of live births	774 (34.3)	776 (34.9)	0.827	0.011
History of abortions	812 (36.0)	800 (35.9)	0.974	0.002
Male factor infertility	782 (34.7)	771 (34.6)	0.976	0.002
Tubal obstruction	142 (6.3)	126 (5.7)	0.628	0.026
Hydrosalpinx	19 (0.9)	16 (0.7)	0.765	0.013
History of pelvic surgery	279 (12.4)	282 (12.7)	0.848	0.01
Pelvic adhesion	56 (2.5)	62 (2.8)	0.679	0.02

Continuous variables are presented as mean (SD) and categorical data are shown as n (%). $p \geq 0.05$ and SMD < 0.1 are regarded as achieving balance. After the IPTW treatment, the number of study populations changed and non-integer values were rounded to the nearest whole number. It is thus clear that all variables are in equilibrium after weighted them

were observed in the 1200 mg/d high-dose VAG group [33]. However, more studies have shown similar pregnancy outcomes of two methods in both fresh and frozen embryo transfers [26–28, 34]. Due to its ease of use, fast absorption, and minimal side effects, VAG seems to be a better alternative. Here, we must consider a question: can VAG really replace IMP in frozen embryo cycles under any circumstances?

Unlike previous studies, our study focused on a specific infertility factor: chronic salpingitis. Since tubal infertility is the most prevalent cause of female infertility, many patients undergoing vitrified-warmed embryo transfer suffer from various tubal lesions, leading to chronic salpingitis. The primary methods of luteal support for such patients remain IMP and VAG, which does not differ significantly from others. Thus, given the high prevalence of tubal infertility and the fact that chronic salpingitis is a key contributor, we sought to investigate whether there are any differences in pregnancy outcomes between two commonly used luteal support methods, IMP and VAG, in this particular patient group.

The results of our study showed that the difference between two regimens occurred mainly in the early pregnancy stage after clinical pregnancy. Commissairea's study [35] showed that serum progesterone levels were significantly lower in patients with early pregnancy loss

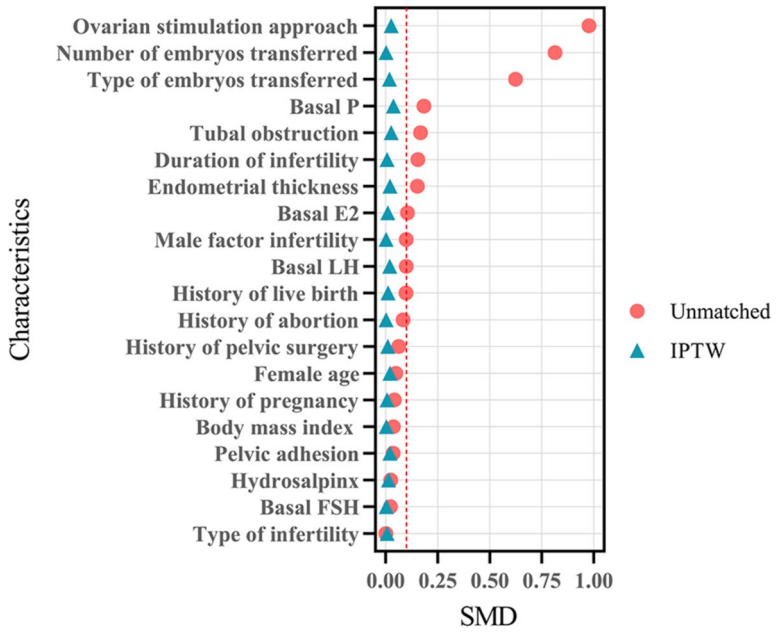

Fig. 2 SMD values of baseline characteristics for two groups before and after IPTW weighting

Table 3 Comparison of the reproductive outcomes between IMP group and VAG group

Outcome	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*p* value
Live birth rate	1.25 (1.017–1.537)	0.034[a]	1.256 (1.019–1.547)	0.033[a]
Biochemical pregnancy rate	0.923 (0.749–1.136)	0.448	0.925 (0.751–1.14)	0.466
Clinical pregnancy rate	0.943 (0.769–1.157)	0.576	0.944 (0.769–1.159)	0.584
Ongoing pregnancy rate	1.231 (1.002–1.512)	0.047[a]	1.236 (1.004–1.521)	0.046[a]
Twin pregnancy rate	1.055 (0.758–1.47)	0.75	1.071 (0.757–1.517)	0.698
Miscarriage rate	0.612 (0.461–0.812)	< 0.001[a]	0.588 (0.443–0.782)	< 0.001[a]
Preterm delivery rate	0.788(0.493–1.258)	0.317	0.841 (0.526–1.344)	0.468
Full-term delivery rate	1.266(0.795–2.015)	0.319	1.191 (0.748–1.895)	0.46

OR: odds ratio; 95% CI: 95% confidence interval

p value < 0.05 was considered statistically significant

[a] Statistically significant

(EPL) than in those with ongoing pregnancy, which may be related to the lack of appropriate luteal support. Given this view, the difference in ongoing pregnancy rate might be due to the discrepancy in absorption efficiency between two luteal support methods, eventually resulting in varying serum progesterone levels. In general, the uterine first-pass effect of progesterone administered vaginally generates high local concentrations in the endometrial tissue, thus avoiding the systemic adverse effects caused by high blood drug concentration [36, 37]. However, the targeted effect of vaginal progesterone to the uterus and the process of absorption and recirculation to the endometrium via intravaginal capillaries are influenced by many factors. Inflammation of the fallopian tubes and pelvic cavity may affect pelvic absorption through the route of vaginal administration, leading to low overall levels of progesterone in patients. Furthermore, in cases of chronic salpingitis, the vaginal mucosa may become more sensitive, resulting in reduced tolerance to vaginally administered medications. This can lead to discomfort, irritation, or other local adverse effects, potentially compromising treatment adherence. In addition, patients with chronic salpingitis are already at an increased risk of infection. VAG may potentially increase the chance of ascending infections, which could further impair pregnancy outcomes. Conversely, IMP, although its side effects are greater than VAG, ensures that the overall blood progesterone level can reach a

stable effective concentration for a long time, and may be less affected by local factors of fallopian tubes and pelvic cavity. IMP also minimizes the risk of local side effects and improves patient comfort and compliance with the treatment protocol. By reducing the likelihood of infection, IMP may provide a more favorable environment for embryo implantation and pregnancy maintenance.

Yet it's worth noting that we are uncertain whether this difference between two groups is related to the medication concentration. Currently, there is no consensus on the optimal dosage of progesterone for various regimens during luteal support. As the most used protocol for luteal support, IMP is usually administered at doses typically ranging from 50 to 100 mg/d [27]. Different from IMP, vaginal progesterone is mainly administered in three forms: gel, tablets, and capsules, and the dosage of each administration varies widely. In this study, we used Crinone vaginal progesterone gel 8% and gave luteal support at a dose of 90 mg once daily, which was consistent with the previously recommended dose [34]. Some researchers also administered Crinone 8% at a dose of 90 mg twice a day, but the results showed no difference in pregnancy outcomes compared to IMP group [26, 38]. However, compared to 90 mg VAG once daily, receiving 90 mg VAG twice a day could significantly improve delivery rate and reduce miscarriage rate after frozen embryo transfer [39]. Therefore, the dosage of progesterone during luteal support may also be an important factor influencing pregnancy outcomes. Our study showed 60 mg/d IMP was significantly better than 90 mg/d VAG due to its better pregnancy outcomes. But it is still not clear whether doubling the dosage of VAG or changing the dosage of two regimens would have altered the difference in final pregnancy outcomes between the two. This may also be one of the directions for our subsequent studies.

This study had several significant strengths. It was conducted at a single center, thus ensuring that therapies for each patient receiving FET were strictly in accordance with the clinical standard guidelines we had established. We also had a unified and standardized laboratory operation system for embryo cryopreservation and thawing. In addition, a relatively large sample size was included in our study over the past 8 years and we fully considered the interference of various confounding factors. As there was an imbalance in the baseline between two groups, IPTW was used to minimize the effects of various confounding factors without reducing the sample size. This study was the first to compare and analyze two luteal support regimens for a specific infertility factor, which had important guiding value for clinicians' medication use.

However, due to the retrospective design of this study, there are several important limitations that must be considered. First, the allocation of patients to either the IMP group or VAG group was determined by physician's judgment and patient's choice, which introduces a potential selection bias that may affect the comparability of the two groups. In addition, although IPTW was carried out to balance the baseline and multivariate logistic regression models were used to adjust for confounders, there may still be unidentified or unmeasured confounders that could influence the observed pregnancy outcomes. Factors such as lifestyles or subtle clinical differences might have affected outcomes in ways that were not captured in the data. Furthermore, in the analysis of pregnancy outcomes, comparisons of neonatal outcomes, such as birth weight, gestational age, or any potential complications, were missing to comprehensively evaluate the impact of two luteal support regimens. The lack of neonatal data restricted the evaluation of long-term reproductive and developmental outcomes, making it difficult to fully understand the potential benefits or risks associated with each protocol. Moreover, because this study was conducted only at a single reproductive center, the results cannot be generalized to other centers and regions. Additional large-scale multicenter prospective clinical trials are needed to confirm the findings and to ensure that the conclusions can be applied more broadly across diverse clinical settings. Finally, the underlying biological mechanisms of IMP and VAG regimens leading to different reproductive outcomes in patients with tubal factor infertility also need to be further investigated.

Conclusion

For patients with chronic salpingitis undergoing vitrified-warmed embryo transfer, our retrospective analysis suggested that intramuscular progesterone for luteal support may be associated with better pregnancy outcomes. Progesterone vaginal gel may be not recommended as an alternative regimen. These findings, based on our 8-year-long retrospective experience, may provide useful insights into luteal support options for infertile patients with tubal factors. Further studies are needed to confirm these results and provide clearer clinical recommendations.

Abbreviations

95% CI	95% Confidence intervals
ART	Assisted reproductive technologies
BMI	Body mass index
BS	Basic solution
CC	Clomiphene citrate
COH	Controlled ovarian hyperstimulation
DS	Dilution solution
E2	Estradiol
EPL	Early pregnancy loss
ES	Equilibration solution
FET	Frozen-thawed embryo transfer
GnRH-a	Gonadotropin-releasing hormone agonist
GnRH-ant	Gonadotropin-releasing hormone antagonist
HCG	Human chorionic gonadotropin

HMG	Human menopausal gonadotropin
HRC	Hormone replacement cycle
HRT	Hormone replacement therapy
IMP	Intramuscular progesterone
IPTW	Inverse probability of treatment weighting
IVF	In vitro fertilization
LH	Luteinizing hormone
OHSS	Ovarian hyperstimulation syndrome
OR	Odds ratio
P	Progesterone
PID	Pelvic inflammatory disease
rhFSH	Recombinant human follicle stimulating hormone
RIF	Recurrent implantation failure
RPL	Recurrent pregnancy loss
SD	Standard deviation
SMD	Standardized mean differences
TS	Thawing solution
VAG	Vaginal gel
VS	Vitrification solution
WS	Washing solution

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Author contributions
Y.L. proposed the idea of the study, performed the analysis of the data, and wrote the manuscript. L.Y. and H.P. added to the idea of the study, completed the data organization and screening, and prepared the manuscript. B.M. provided the raw data for the study and critically revised the manuscript. Z.Z. supervised and guided the whole process of the study and reviewed and edited the manuscript. Q.Z. conducted an evaluation of the research quality. L.L. and Y.J. provided the methods and R scripts for the statistical analyses in this study. L.M. and Z.X. searched the corresponding literature. All authors read and approved the final manuscript.

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Availability of data and materials
The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Xuzhou Maternity and Child Health Care Hospital on 31 October 2023 and was guided by the principles of the Helsinki Declaration. According to institutional standards, written informed consent for participation was not necessary for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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