

Live-Birth Outcomes and Congenital Malformations After Progesterin-Primed Ovarian Stimulation in Maternal Endometriosis

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Purpose: In patients who had advanced endometriosis, we use different protocols including GnRH agonist, GnRH antagonist and progesterin-primed ovarian stimulation (PPOS) protocols to assess live-birth congenital malformations delivered after in vitro fertilization (IVF) and vitrified embryo transfer cycles.

Methods: A retrospective cohort study is conducted by us. It includes 1495 live-born infants in maternal endometriosis. From January 2010 to January 2017, we brought into infants who underwent either gonadotropin-releasing hormone agonist long protocol, gonadotropin-releasing hormone antagonist protocol or PPOS. We chose neonatal outcomes and congenital malformations as our major measures.

Results: Neonatal outcomes, as well as congenital malformations, were considered as the main measures, and gestational age, birth weight, birth length, multiple births and early neonatal death are included. All groups were comparable. The GnRH antagonist group (1.41%) and the GnRH antagonist protocol group (1.8%) had the same incidence of live-birth defects as the PPOS groups (1.33%) were similar. There were no apparent differences when it came to congenital malformations among the three groups. Multivariate logistic regression showed that infertility-time factors as well as multiple births combined to add the risk of congenital malformations; the adjusted odds were 1.143 (95% confidence interval [CI]: 0.988–1.323) and 3.253 (95% CI: 1.359–7.788). Besides, no association was found among various ovarian stimulations as well as congenital birth defect programs, maternal age, body mass index, parity or infant sex.

Conclusion: This study suggests that, in contrast to conventional ovarian stimulation, PPOS neither has any effect on neonatal outcomes in IVF adverse effects nor does it elevate the rate of congenital malformations in late endometriosis. However, randomized controlled trials of the long-term outcomes of children born after PPOS protocols for maternal endometriosis are needed and the follow-up studies were conducted to confirm this result.

Keywords: medroxyprogesterone acetate, congenital malformation, in vitro fertilization, live birth, endometriosis

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Introduction

Endometriosis, a female disorder, is characterized by endometrial glands or stroma which are outside the uterine cavity. The lesion is usually localized in the peritoneum or ovaries. Among all conditions, endometriosis stands out as one of the most demanding ones for doctors who work on conceiving infertile women. At present, many theories exist to attempt to explain its cause. Some draw on Retrograde menstruation/Sampson's theory, coelomic metaplasia, lymphatic spread, spread

via pelvic veins, surgical transplantation, induction theory, stem cell theory and activation of Müllerian cell in resting state.

According to previous relevant studies, infertility in patients who suffer from endometriosis is primarily due to reduced ovarian reserve and ovarian response, higher FSH levels, lower levels of anti-Müllerian hormones, and abnormal protein expression. Besides, patients who suffer from endometriosis have increased production of cytokines and inflammatory factors, inducing endocrine and paracrine and autocrine pathways are altered, which may contribute to the reduced implantation rate. There are some observed changes in maternal endometriosis, they could lead to low oocyte quality and reduced implantation capacity.^{1,2}

During pregnancy and childbirth, women who suffer from endometriosis in advanced condition have a higher tendency to a number of adverse outcomes. What is worse, they are at a higher risk of other conditions such as premature birth, congenital malformations and neonatal death.³ For women suffering from endometriosis, while the disease has its incidence peaked during the reproductive years and endometriosis can complicate conception as well as pregnancy, and the health of their children has caught more attention recently. Newly released research has found that women with endometriosis have an inclined tendency to have pregnancy complications, which include miscarriage as well as ectopic pregnancy.⁴ Furthermore, according to the literature, women, who suffer from endometriosis would face with a higher tendency of preterm birth,^{5–8} even though conflicting results exist.^{9,10}

IVF is considered as a common method in dealing with maternal endometriosis-related infertility. The use of IVF-ET has the possibility to bypass the suspected dysfunction of endometriosis affecting the natural cycle described above. It has been suggested that IVF is less effective in endometriosis cases than in other indications,¹⁸ nevertheless, a number of articles and national registries prove that IVF can provide the same effect for endometriosis.¹¹

During the last decade, ART technique has made great strides. One most significant aspect is to control the LH spike in non-downregulated COH cycles.^{12–15} In 2009 and 2015, we had relevant reports on the efficiency and feasibility of luteal phase stimulation as well as PPOS protocol. Moreover, their safety of the offsprings was also reported.^{16–19}

In 2017, we reported on oocyte quality and implantation rate by using PPOS for maternal endometriosis. The

rate is comparable to that of the GnRH-agonist regimen. Since this regimen has benefited more than a thousand children with maternal endometriosis, it is important to report these, given its safety data for infants with endometriosis.

This study is designed with the aim of a comparison between live-birth outcomes and defects born after in vitro fertilization (IVF) as well as vitrified embryo transfer cycles with the use of PPOS treatment with conventional protocols in women with advanced endometriosis. As it is mostly used worldwide, the GnRH agonist and antagonist protocols were chosen and applied in the control groups with the purpose to assess the safety of those born to PPOS.

Materials and Methods

Study Population and Design

This study was conducted in accordance with the Declaration of Helsinki. At the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine, we conducted a retrospective cohort study that was approved by the ethics committee of the hospital. Infertile patients with endometriosis recruited at our center went through IVF or intracytoplasmic sperm injection (ICSI) treatment, with the use of PPOS protocol, GnRHa agonist protocols or antagonist protocols for frozen and later on thawed embryo transfer (FET). Written informed consent is given by the participants after we described the whole study in great detail.

They all suffered from endometriosis, which was diagnosed by laparoscopic or abdominal surgery. According to the American Fertility Society's revised classification (1997), endometriosis was scored.

These patients had gone through the procedures from January 1, 2010 to January 1, 2017, and they were expected to give births between November 1, 2010 and November 1, 2017. As these factors may be associated with birth defects, this analysis excludes reported cases of gestational diabetes, hypertension, thyroid disease, and babies born to mothers with maternal diseases or exposed to adverse environmental conditions during the period of pregnancy.

Birth defects were defined and coded according to the International Classification of Diseases, 10th Revision (ICD-10). Minor birth defects were excluded, except those that required treatment or were disfiguring. The

cases with several birth defects were counted as one case in each subgroup, but they could be assigned to more than one subgroup.

Ovarian Stimulation Protocols

In the PPOS group, each day patients were injected with human menopausal gonadotropin (hMG; Anhui Fengyuan Pharmaceutical Co. Ltd) of 150–225 IU and MPA 10 mg daily till the trigger day. Follicular monitoring got performed every 2 to 4 days starting from MC9-11; also, serum at the final stage of oocyte maturation was measured FSH, LH, E2 and progesterone concentrations.

In the GnRH agonist treatment group, the dosage of gonadotropins was determined based on patient characteristics such as age, serum hormone levels, and number of antral follicles in the anterior chamber. Patients undergo a continuous transvaginal ultrasound and hormone monitoring during periods of hyperstimulation.

In the GnRH antagonist treatment group, the starting dose of gonadotropin was 150–225 IU of hMG. Day 2 or 3 saw the start of stimulation of the menstrual cycle and there was a commenced GnRH antagonist on Day 5 of stimulation (certrotide 0.25 mg, Baxter). On day 8 or 9 of stimulation, a pelvic ultrasound and serum hormone assessment were performed.

Ovarian response was assessed through ultrasound and serum E2 levels. When 1–3 follicles reached 18 mm in diameter, for PPOS groups and GnRH antagonist groups, alone or with 1000–5000 IU of hCG (Zhuhai Lizhu Pharmaceutical Group Company) co-triggered the final stage of oocyte maturation. For the GnRH agonist protocol group, we set 5000 IU of hCG (Zhuhai Lizhu Pharmaceutical Group Inc).

Oocyte retrieval was undertaken within 32–36 hours following maturation induction or ovarian stimulation (depending on the protocol per group). Conventional IVF was carried out in females who had indications for tubal or idiopathic infertility, and ICSI was carried out for male factor indications. Culture, as well as scoring of embryos, was in accordance with the previous description. Embryo freezing and thawing procedures, methods of synchronization of embryos and endometrium during natural, ovulation-stimulated, or artificial cycles; and the timing of FET is described elsewhere. Once pregnant, progesterone (P) supplementation would be continued till 10-week gestation.

Follow-Up and Definitions

According to the definition used by the World Health Organization, the term live birth is a delivery with any evidence of life, despite the gestational length. The assessment details of birth defects have been shown in a formerly published paper. In brief, newborns born in our hospital undergo routine medical examinations at birth, and those born in other hospitals are attended by a written health report, which is provided by the pediatrician. Birth defects are defined and coded under the 10th revision of the International Classification of Diseases (ICD-10).

According to the definition, gestational age refers to the age of the embryo or fetus and is calculated as the number of full weeks since fertilization plus 14 days (for FETs, estimated Fertilization date was calculated by subtracting the embryo age from the FET cycle transfer date on the cryopreservation date). Preterm birth (PTB) and very premature birth (VPTB) were considered as deliveries prior to 37 and 32 weeks of gestation, respectively. Low birth weight (LBW) and very low birth weight (VLBW) were considered as <2500 g and <1500 g, respectively. Stillbirth was identified as Intrauterine or intrapartum death of an infant ≥ 20 weeks gestation or birth weight ≥ 500 g, with early neonatal death being defined as live-born babies' death within 7 days of birth.

Statistical Analysis

Statistics was analyzed using SPSS 17.0 software (SPSS Inc.). Data are expressed as mean $\pm$ SD if the data are normally distributed, or as median (range) are expressed; qualitative data are expressed as percentage indicated. Mean differences in continuous parameter data were defined by one-way ANOVA or Kruskal–Wallis test, and differences of the means amid the three groups of Ratios were compared using χ^2 test or Fisher's exact test, as appropriate. Binary logistic regression was performed to quantify the effect of risk factors on congenital malformations between groups. The effect generated by risk factors on congenital malformations by adjusted odds ratio (OR) and 95% confidence interval (CI) indicated. Multivariate logistic regression analysis was used to assess the association of congenital malformations with maternal age, duration of infertility, parity, ovarian stimulation method, multiple birth, and infant gender.

Results

Pregnancies and Deliveries Outcomes

A total of 1398 continued gestational cycles resulted in 1495 births. Out of these, 1108 continued pregnancies

(gestational weeks ≥ 20 weeks) resulted in 1203 infants treated with PPOS. Of the 221 infants, 215 from ongoing pregnancies were born after receiving the GnRH agonist regimen treatment. Seventy-one infants resulting from 75 ongoing pregnancies were born after receiving GnRH antagonist stimulation. These results imply that each of the three ovarian stimulation regimens had a significant proportion of pregnancies resulting in live births of infants (The flowcharts in Figure 1 and Table 1 provide a detailed overview of the distribution of the groups.).

Major parameters which include maternal age, infertility duration, BMI, gestational age, birth weight, birth length, embryo transfer date as well as multiple delivery rates were all considered comparable between the groups.

Totally, 21 (1.40%) of all live births were consistent with congenital defects, as defined by the International Classification of Diseases. HMG and 16 of 1203 cases (1.33%) in the MPA group were defective, 4 of 221 cases in the GnRH agonist protocol group (1.80%) and

1 of 71 cases (1.41%) in the GnRH antagonist group had defects, with no significant difference. The comparison between birth defect groups according to neonatal sex, singleton and multiple births is shown in Table 2.

Table 3 shows in detail the breakdown of the detected malformations under different organ systems. The results showed that relatively higher percentages of cardiac defects (0.47%) and musculoskeletal system problems (0.20%) were observed.

Table 4 shows the results of logistic regression of factors potentially influencing congenital malformations. The binary logistic regression was used for the analysis of treatment as well as patient characteristics for risk factors related to adverse outcomes for risk factors, including maternal age, BMI, infertility duration, parity, multiple births, gender of infants, and ovarian stimulation protocol. Multiple births (X_1), BMI (X_2), and infertility duration (X_3) were contained within the logistic regression equation as: $\text{logit } P = -2.382 + 0.872X_1 - 0.113X_2 - 0.163X_3$. The

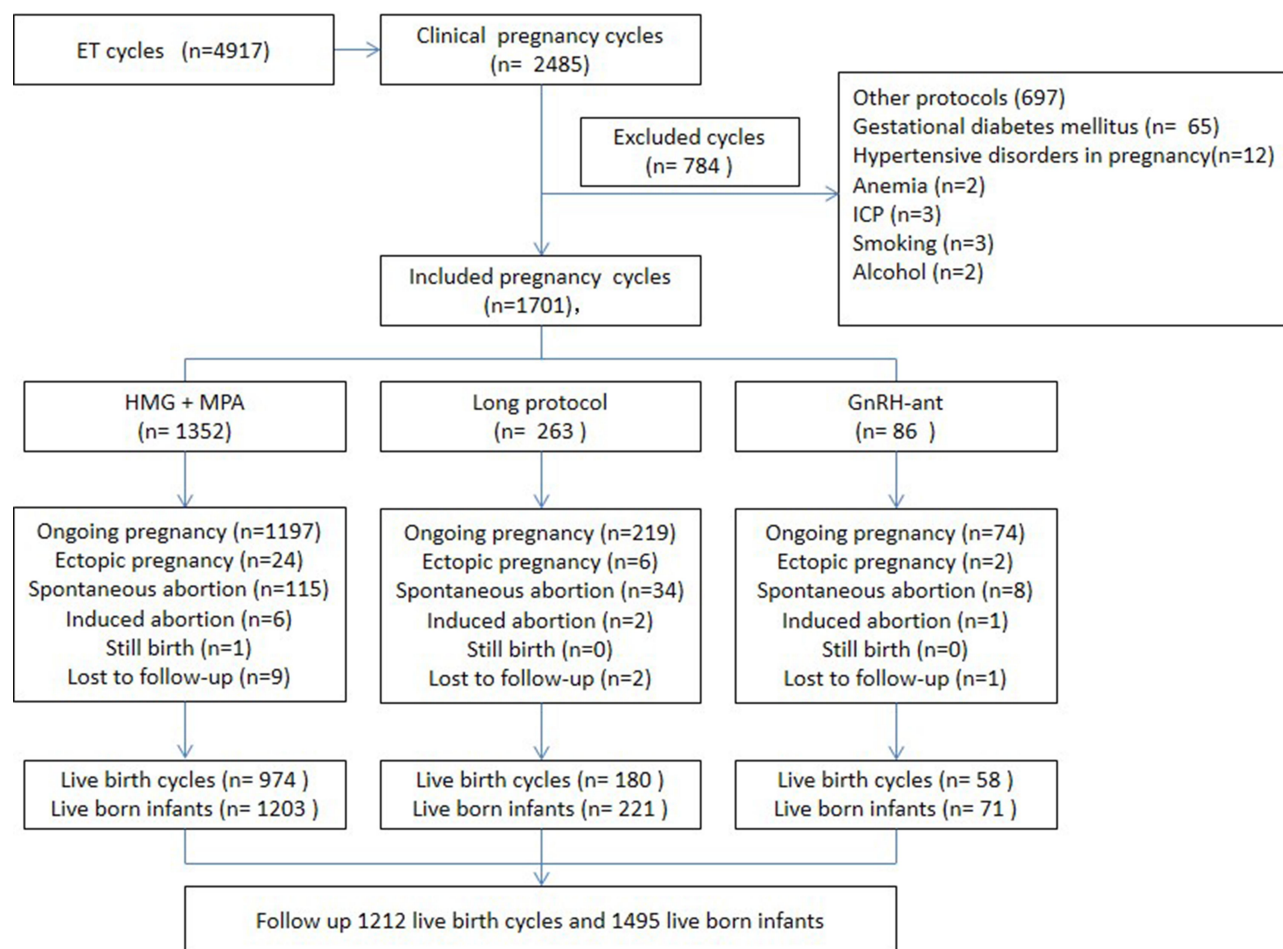


Figure 1 Flowchart of the study.

Table 1 Characteristics and Neonatal Outcome by Regimen Group

	PPOS (n=974)	GnRH Agonist (n=180)	GnRH Antagonist (n=58)	F/ χ^2	P value
Maternal age (years)	34.48±3.87	34.7±3.59	34.45±2.76	0.942	0.487
Infertility duration	3.185±2.35	3.383±2.15	3.536±2.44	0.973	0.379
Body mass index	20.77±3.30	20.66±3.42	20.29±4.51	0.585	0.558
Pregnancies					
0	656(67.3)	117(65.0)	37(63.8)	0.124	0.938
1	195(20.0)	40(22.2)	15(25.9)	0.945	0.625
≥ 2	123(12.7)	23(12.8)	6(10.3)	0.216	0.898
Total Ets	1803	357	107	–	–
Embryos from IVF cycles	1257(69.7)	242(67.8)	72(67.3)	0.735	0.693
Embryos from ICSI cycles	546(30.3)	115(32.2)	35(32.7)	0.735	0.693
Cleavage-stage embryos	1602(88.9)	315 (88.2)	96 (89.7)	0.210	0.900
Blastocyst embryos	201(11.1)	42(11.8)	11(10.3)	0.210	0.900
Live-born infants	1203	221	71	–	–
Gestational age	37.92±2.07	37.63±2.22	37.95±1.74	0.945	0.389
<32	12(1.2)	3(1.7)	0(0)	0.981	0.612
32 ≤ age < 37	638(65.5)	99(55.0)	32(55.1)	2.101	0.350
≥ 37	324(33.3)	78(43.3)	26(44.9)	4.182	0.124
Birth weight (g)	3145±609.2	3163±577.2	3180±499.5	0.124	0.884
Birth length	49.5±2.38	49.24±2.22	49.59±1.85	0.443	0.642
Multiple delivery cycles	230(23.6)	42(23.3)	14(24.1)	–	–
Multiple delivery rate	23.6	23.3	24.1	0.010	0.995
Early neonatal death	4(0.4)	1(0.5)	1(1.7)	1.893	0.388

probability of adverse outcomes was significantly increased in both models for infertility duration and multiple births.

Discussion

More than 150 million women worldwide are affected by endometriosis. According to estimation, 7–12% of reproductive-aged women are affected. The prevalence is even higher among infertile women. It affects as many as a quarter of patients treated with ART and 20–40% of them develop ovarian endometriosis.^{20,21}

Although there is no causal relationship, possible pathways of infertility due to endometriosis involve endocrine as well as ovulatory abnormalities,²² effects on oocytes and sperm,²³ inflammation/altered peritoneal environment, distorted pelvic anatomy,²⁴ abnormal uterine transport, altered hormonal and cell-mediated function,²⁵ impaired implantation and other unknown mechanisms.^{26–28}

IVF is considered effective in treating endometriosis in infertile women even though its rate of success may be affected by the disease on its own.

In women who suffer from endometriosis, MRI scans and biopsies reveal abnormalities in the function and

Table 2 Incidence of Birth Defects in Live-Born Infants

Characteristics	PPOS (n=1203)	GnRH Agonist(n=221)	GnRH-Antagonist (n=71)	χ^2	P value
Number of birth defects	16 (1.33)	4 (1.81)	1 (1.41)	0.301	0.860
Number of deliveries					
Singletons	6 (0.50)	2 (1.81)	1 (1.41)	1.604	0.448
Multiples	10 (0.83)	2 (1.81)	0 (0)		
Birth defects, by gender					
Male	9 (0.75)	2 (1.81)	0 (0)	1.205	0.547
Female	7 (0.58)	2 (1.81)	1 (1.41)		

Notes: Data are n (%) and were compared using Fisher's exact test. N=1495.

Table 3 Types of Malformations Among 1495 Live-Born Infants

Total	PPOS (n=1203)	GnRH Agonist (n=221)	GnRH Antagonist (n=71)
	16(1.33)	4(1.80)	1(1.41)
Nervous system (Q00–Q07)	0	0	0
Eye, ear, face and neck (Q10–Q18)	0	0	0
Circulatory system (Q20–Q28)	7(0.58)	0	0
Respiratory system (Q30–Q34)	0	1(0.45)	1(1.41)
Cleft lip and cleft palate (Q35–Q37)	2(0.17)	0	0
Digestive system (Q38–Q45)	0	0	0
Genital organs (Q50–Q56)	1(0.08)	0	0
Urinary system (Q60–Q64)	2(0.17)	0	0
Musculoskeletal system (Q65–Q79)	2(0.17)	1(0.45)	0
Other malformations (Q80–Q89)	1(0.08)	2(0.90)	0
Chromosomal anomalies (Q90–Q99)	1(0.08)	0	0

Table 4 Logistic Regression for Factors Influenced Congenital Malformations

Variables	Coefficient (B)	OR (95% CI)	Wald(χ^2)	P value
Unadjusted model				
Maternal age	−0.090	0.913(0.803 – 1.040)	1.878	0.171
BMI	−0.106	0.900(0.742 – 1.091)	1.152	0.283
Infertility duration	0.199	1.220(1.029 – 1.446)	5.264	0.022
Parity	0.378	1.459(0.187 – 11.388)	0.130	0.718
Multiple births	1.017	2.765(1.128 – 6.778)	4.943	0.026
Gender of infants	0.692	1.997(0.706 – 5.649)	1.701	0.192
GnRH agonist protocol	−0.863	0.422(0.054 – 3.316)	0.673	0.412
Antagonist protocol	−17.032	0.000	0.000	0.997
Adjusted model				
BMI	−0.119	0.888(0.728 – 1.082)	1.388	0.239
Infertility duration	0.134	1.143(0.988 – 1.323)	3.232	0.072
Multiple births	1.180	3.253(1.359 – 7.788)	7.015	0.008

structure of the lining of the uterus, called junctional zone, which means endometriosis is associated with adenomyosis, a junctional zone disease. It could lead to transformation defects in the spiral arteries, which can influence placentation thereby.²⁹ It has already become a theory that this has the possibility to result in a greater risk of preeclampsia, intrauterine growth restriction, preterm labor and placental abruption.³⁰

We introduced PPOS protocols not merely because, compared to GnRH agonist and antagonist protocols, PPOS options are not unfavorable regarding pregnancy and implantation rates. What is more important, it could also offer a more economical and patient-friendly therapeutic option.

Generally, the congenital malformation rate, which is 1.4% shown in this study, is similar to 1.11–1.58% in

a Chinese study, which is a population-based one. The rate of birth defects occurring within 7 days of delivery is consistent with that of IVF.³¹ Our cohort study proves that among all organ systems, the cardiovascular system has the highest frequency to be affected by congenital malformations, which is also consistent with previous studies.

Some studies have discussed the maternal factors' influence on congenital malformation. Only two studies previously focused on the boys having anomalies with their genitals among boys delivered by women having endometriosis (without IVF). Possible linkage with specific factors from the maternal angle and the genital anomaly cryptorchidism (undescended testis) was investigated by a case-control study by Mavrogenis in 2014.³² The investigators in that study determined that the risk of

cryptorchidism among sons born to mothers with endometriosis was double. Nevertheless, a register-based Danish study in 2017 revealed the lack of any substantial evidence for the greater incidence of endometriosis-afflicted women giving birth to boys with genital anomalies.³³

Congenital malformations are observed more commonly in twin pregnancies than in singleton pregnancies.^{34,35} Some studies show that twins are about four times more likely to have congenital malformations than singletons.³⁶ These congenital abnormalities could come from twinning itself, from vascular connections between the twins or compression deformation from uterine crowding. Developmental disorders can occur during twinning, too, which may lead to susceptibility to environmental factors.³⁷

As the use of fertility drugs increases and assisted reproduction technology gets improved, the twinning rate has also grown, which could also give rise to an increasingly higher frequency of congenital defects. Previous studies show a significantly grown risk of multiple birth defects, including inadequate nutritional supply, common genetic background and crowded uterine conditions.^{38,39}

Some limitations do exist in this study. There are several possible reasons as to why the birth defect rate in this study is lower, they are: (1) The congenital malformation rate was determined with the use of both living newborns and terminated pregnancies, which means that the data are not comprehensive enough to provide a representation of the entire spectrum of birth defects, for example, those linked to miscarriages and stillbirths. As a result, it is possible that the real rate of congenital malformations is higher than our data implies. (2) We purposefully restricted participants to women who had experienced no reported cases of maternal disease or negative environmental exposures in the course of pregnancy, enabling us to more precisely evaluate the isolated effects of different types of ovarian stimulation regimens regarding subsequent neonatal outcomes. (3) We collected neonatal outcome data through questionnaires of patients instead of direct review of medical records. (4) In this study, though the sample size is comparatively large, it may have limited statistical power in detecting disparities among such rare outcome measures like congenital malformations. Nevertheless, the findings of our data are reassuring, as many other confounding variables remain unchanged. (5) In this study, the infants were all born from FET cycles, which were considered to have a less degree of risk-concerned birth defects, in comparison with fresh ET cycles.]

This study shows that, compared to the other two ovarian stimulation maternal endometriosis protocols, infants born after PPOS protocols embrace no notable distinctions in neonatal outcomes or congenital malformations. This means that the regimen could be safe while effective alternative to the conventional one for the birth of women with endometriosis. Nonetheless, a proper randomized study is needed to evaluate, as well as to further validate if this new ovarian stimulation protocol is safe and effective in women with endometriosis.

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Author Contributions

Y.W. supervised the entire study, including the procedures, conception, design and completion. Z.L. was responsible for the collection of data. Z.L. contributed the data analysis and drafted the article. Y.P.K participated in the interpretation of the study data and revisions to the article. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

None of the authors have any conflicts of interest to declare.

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