Impact of different menstrual lengths in antagonist regimens on IVF assistance and pregnancy outcomes

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Abstract

Objective: To compare whether there is a difference between the two groups of patients with different menstrual lengths in the antagonist regimen in terms of controlled ovarian stimulation（COS） and pregnancy outcome.

Methods: In a retrospective analysis, case data of patients receiving IVF/ICSI assisted conception in the Department of Human Assistive Technology at the Affiliated Hospital of Southwestern Medical University from August 2018 to August 2021 were included and classified as having periods ≤4 days (n=103) and periods >4 days (n=442) based on the length of menstrual periods. basic information, ovulation procedures, laboratory data, and pregnancy outcomes were compared between the different menstrual length groups. Patients who achieved pregnancy were further divided into 2 groups according to the length of menstruation, and the mode of delivery and complications were recorded separately between the groups. Women were followed up until delivery and divided into different menstrual groups, the number of weeks of delivery, infant length, and infant weight were analyzed in both groups.

Result(s):A total of 545 patients were assisted with antagonist regimens for pregnancy, based on the length of periods, divided into those with periods ≤4 days (n=103), those with periods >4 days (n=442).With no difference in age, the patients with periods >4 days had lower FSH/LH than those with periods ≤4 days (2.60 (1.80 to 3.58) vs. 3.57 (2.58 to 8.33), p<0.05) ,In contrast, AMH was higher (2.25 (1.18-3.83) vs. 1.73 (1.12-3.17), p < 0.05).We could deduce that ovarian reserve function may be better in patients with >4 days of menstruation than in those with ≤4 days of menstruation.We could deduce that ovarian reserve function may be better in patients with >4 days of menstruation than in patients with ≤4 days of menstruation, as evidenced by the fact that the initiation dose (bottles) (4(3-4) vs 3(2-4), p<0.05) and total Gn dose (bottles) (36.00(28.00-40.00) vs 32.00(24.92-40.00), p<0.05) were significantly higher in patients with ≤4 days of menstruation than in patients with >4 days of menstruation during in vitro fertilization. While the number of eggs obtained (7.00 (5.00-10.00) vs. 8.00 (6.00-11.25), p < 0.05), the number of MII (7.00 (4.00-10.00) vs. 8.00 (5.00-11.00), p < 0.05), and the number of 2PN (4.00 (3.00-6.00) vs. 5.00 (3.00-8.00), p < 0.05) yet lower than in patients with periods >4 days.During transplantation and post-transplantation follow-up, it was found that patients with periods >4 days had thicker endometrium (mm) at transplantation day than those with periods ≤4 days (9.10 (7.60-10.10) vs. 10.80 (9.50-12.30), p < 0.05), clinical pregnancy and biochemical pregnancy with periods >4 days were higher than those with periods ≤4 days (169 (38.2%) vs. 34 (33.0%)), (59(13.3%) vs 6(5.8%)), and non-pregnant patients with periods ≤4 days were higher than those with periods >4 days (63(61,.2%) vs 214(48.4%)) with statistical significance (p=0.027, <0.05). There was no statistically significant difference between the two groups with different menstrual periods for mode of delivery, ectopic pregnancy, early miscarriage, late miscarriage, week of gestation of delivery, fetal weight and fetal length in patients after fresh embryo transfer with antagonist regimen.

Conclusions: From this retrospective study,it can be deduced that the sensitivity of patients with <4 days of menstruation to pro-ovulatory drugs,the number of eggs obtained by pro-ovulation,the thickness of the

endometrium on the transplantation day,and the pregnancy outcome (clinical pregnancy, biochemical pregnancy) are lower than those with ≥4 days of menstruation during IVF.

Background

Due to the environmental factors, socio-economic development and increased pressure of life, infertility has become the third most common disease after tumors and cardiovascular accidents[1].In the last 40 years, in vitro fertilization and embryo transfer (IVF-ET) has been an important treatment for patients with infertility, mainly using controlled ovarian hyperstimulation (COH) to obtain eggs in vitro for fertilization and implantation in the uterus, leading to a pregnancy outcome[2].In recent years, antagonist regimens have been used more frequently in ovulation, and their pregnancy outcomes are of great concern due to the absence of a descending regulatory process. success in IVF pregnancies mainly consists of high-quality embryos and synchronous development of the endometrium, and how to improve pregnancy rates and predict pregnancy outcomes has become a hot topic for clinicians to pursue.

We all know that women's menstruation is the result of the cyclical changes of the endometrium by the action of ovarian hormones[3],The normal menstrual period is 2-8 days, and women of childbearing age can still repair without scarring after experiencing bleeding from ruptured small spiral arteries and endometrial apoptosis and exfoliation during menstruation[4].Is it implied that we may have cells in the endometrium that regulate proliferation contributing to altered pregnancy outcomes? Does the length of the menstrual period as an expression of the endometrial repair process have an impact on IVF pregnancy outcome?

We searched the Web of science for "menses" with 5578 items from the database, with a search frequency of 30, showing 586 papers, of which the literature on "menses" was about "progesterone", "estradiol", "bone mineral density", " comolication" and "endometriosis" were more frequent, yet "IVF" was not mentioned or less frequently mentioned. In this retrospective analysis, we investigated whether there were differences in the antagonist regimen and pregnancy outcomes between the two groups by grouping them with different lengths of menstruation(see Figure 1).

Materials And Methods

Retrospective analysis of case data of patients undergoing IVF/ICSI at the Department of Human Assistive Technology, Southwest Medical University Hospital from August 2018 to August 2021, with inclusion criteria: 1) age <40 years; 2) periods of 2-8 days and cycles of 28-32 days; 3) FSH ≤10 mIU/mL and AMH ≥1.1 ng/mL; 4) use of antagonist regimen; 5) recent 3 months without oral contraceptives for pretreatment; 6) fresh cycle embryo transfer was performed. Exclusion criteria: 1) endometriosis, adenomyosis; 2) endometrial polyps, uterine adhesions, congenital uterine dysplasia; 3) chromosomal karyotype abnormalities in either spouse; 4) patients with recurrent miscarriage. A total of 545 patients were included and classified into those with periods ≤4 days (n=103) and those with periods >4 days (n=442) based on the length of periods.

1. **COH:** Initiation of the cycle is started on day 2-4 of menstruation, and the initiation dose is determined by a combination of the patient's age, AFC, BMI, FSH, and AMH levels. rFSH (75/450 U/strike, Gonafine, Merck, German) is used as the initiating drug.When the primary follicle diameter reached 12-14 mm, according to serum estradiol (E2) and luteinizing hormone (LH),gonadotropin-releasing hormone antagonist (GnRH-ant, 0.25 mg/d, Schizophrenia, Merck, Germany) was administered at 0.25-0.5 mg/d .When ≥1 follicle diameter was at least 18 mm, 250ug of Eze (recombinant human chorionic gonadotropin injection, Merck, Germany), and eggs were retrieved at 36-38 h with vaginal ultrasound monitoring.
2. **Embryo transfer:**Progesterone injection (10mg/stem, Zhejiang Xianju) 60mg/d and Dydrogesterone (10mg/tablet, Solvay, Netherlands) 20mg bid were given on the day of egg retrieval. 1-2 good quality embryos were selected for transfer after endometrial thickness was recorded by ultrasound on the 3rd or 5th day after egg retrieval. 14 days after transfer, blood β-HCG was measured to determine pregnancy outcome (non-pregnancy, biochemical pregnancy). Vaginal ultrasound examination on day 28 for gestational sac and visible fetal heartbeat as clinical pregnancy.
3. **Embryo scoring:**Oogenesis Embryo Scoring System Assesses Embryo Quality According to Peter[5]:Cells were scored from cell number, fragmentation classification (fragmentation <10% score 4, 10% <fragmentation <20% score 3, 20% <fragmentation <50% score 2, 50% <fragmentation score 1), and ovoid homogeneity (homogeneity score 1, inhomogeneity score 0).According to the Gaidner scoring system: the criteria for good quality blastocysts were defined as those with stage 3 and above, and both inner cell mass (ICM) and trophoblast (TE) cells of grade B and above[6].
4. **Observed indicators:**Age, BMI, LH, FSH, FSH/LH, AMH, initiation dose (bottless), Gn days, total Gn(bottless), the number of OPU,the number of MII, the number of 2PN, endometrial thickness at transplantation, pregnancy outcome (clinical pregnancy, biochemical pregnancy, non-pregnancy) were recorded for patients in different groups of menstrual length. Patients who obtained pregnancy were then divided into 2 groups according to the length of menstruation, and the mode of delivery (vaginal delivery, cesarean delivery), ectopic pregnancy, early miscarriage, and late miscarriage were recorded between the different groups. Women were followed up until delivery, divided into different menstrual groups, and postpartum outcomes (weeks of delivery, infant length, and infant weight) were recorded.

Statistical Analysis

SPSS 17.0 was used for statistical analysis, and all data were first tested for normality, as the data of age, BMI, LH, FSH, FSH/LH, AMH, AFC, initiation dose (bottles), Gn days, total Gn(bottles), the number of OPU the number of MII, the number of 2PN, endometrial thickness at transplantation, weeks of labor, infant length, and infant weight of patients in different groups is skewed, using median and inter-quartile ranges to describe the data, using a non-parametric test(Mann-Whitney test). For categorical variables Pearson chi-square test was used and Fisher's exact method was used to derive p-values when including

individual data <5. Graph Prism plotted pie charts, histograms and scatter plots. $p < 0.05$ suggested statistical significance.

Results

1.The 545 patients included in the study were divided into those with periods ≤4 days (n=103), those with periods >4 days (n=442), based on the length of their periods.The baseline characteristics are presented in Table1.The varianle is skewed,so we use median and inter-quartile ranges to summarize the data.It can be shown that LH and FSH/LH were higher in patients with ≤4 days of menstruation than in patients with >4 days of menstruation, while FSH and AMH were lower. The initiation dose (bottles) and total Gn dose (bottles) were higher in patients with ≤4 days of menstruation than in patients with >4 days of menstruation, while endometrial thickness, number of eggs gained, MII and 2PN on the transplantation day were lower than in patients with >4 days of menstruation ($p < 0.05$).The AMH histogram is shown in Figure 2, and the scatter plot of endothelial thickness at transplantation day is shown in Figure 3.

Table 1

Comparison of basic information and ovulation promotion process between two groups

menstruation	≤4 days（n=103）	＞4 days（n=442）	Z	P
Age(years)	31（28~36）	31（28~35）	-1.040	0.298
BMI	22.03（19.82~24.29）	22.22（20.06~24.68）	-1.242	0.214
LH (mIU/mL)	9.02（7.63~11.25）	8.40（7.02~10.16）	-2.546	0.011*
FSH (mIU/mL)	2.57（1.47~3.42）	3.32（2.31~4.85）	-5.147	0.000*
FSH/LH	3.57（2.58~8.33）	2.60（1.80~3.58）	-6.003	0.000*
AMH (ng/mL)	1.73（1.12~3.17）	2.25（1.18~3.83）	-2.074	0.038*
initiation dose (bottles)	4（3~4）	3（2~4）	-2.843	0.004*
Gn days	10（9~11）	10（9~11）	-0.205	0.837
total Gn dose (bottles)	36.00（28.00~40.00）	32.00（24.92~40.00）	-2.311	0.021*
endometrial thickness at transplantation(mm)	9.10（7.60~10.10）	10.80（9.50~12.30）	-7.493	0.000*
the number of OPU	7.00（5.00~10.00）	8.00（6.00~11.25）	-2.548	0.011*
the number of MII	7.00（4.00~10.00）	8.00（5.00~11.00）	-2.170	0.030*
the number of 2PN	4.00（3.00~6.00）	5.00（3.00~8.00）	-2.666	0.008*

2.The baseline characteristics are presented in Table2.Pearson chi-square test was used for both groups in their pregnancy outcomes (clinical pregnancy, biochemical pregnancy, and non-pregnancy) respectively.Pearson chi-square value: 7.248, p=0.027 (p<0.05), there was a statistical difference in their pregnancy outcomes (clinical pregnancy, biochemical pregnancy, and non-pregnancy,see Figure 4) between the two different groups. As the column coefficient r=0.115,p=0.027 (p>0.05), it indicates that there is a association between the length of menstruation and pregnancy outcome, but the degree of association is weak.

Table 2

Comparison of pregnancy outcomes and correlation coefficients between the two groups

3.A total of 268 patients who obtained pregnancy through the antagonist regimen were divided into 2 groups according to the duration of menstruation, and the mode of delivery (pie chart see Figure 5), ectopic pregnancy, early miscarriage, and late miscarriage were examined between the different groups

	pregnancy outcomes			Pearson chi-square value:	r	p
	clinical pregnancy	biochemical pregnancy	non-pregnancy			
≤4	34(33.0%)	6(5.8%)	63(61,.2%)	7.248	0.115	0.027*
4	169(38.2%)	59(13.3%)	214(48.4%)			

(see Table 3). Although patients who chose cesarean delivery were obviously higher than those who had vaginal delivery, there were no statistical differences in the mode of delivery, ectopic pregnancy, early miscarriage, and late miscarriage between the different groups.

Table 3

Comparison of the data related to pregnancy outcomes

	≤4 day	4 days	Pearson chi-square value	P
Cesarean delivery	15(12.93%)	101(87.07%)	0.824	0.364
Vaginal delivery	6(19.35%)	25(80.65%)		
Ectopic pregnancy	2(33.3%)	4(66.7%)	1.638	0.201
Early miscarriage	3(16.7%)	15(83.8%)	0.046	0.830
Late miscarriage	0(0%)	2(100%)		1.000#

Note:#:Because of the inclusion of individual data <5, Fisher's exact method was used to derive p-values.

4.A total of 121 patients (26 of whom were twins) were followed up to delivery in women by antagonist regimen fresh embryo transfer (pie chart see Figure 6) according to the number of deliveries, a total of 147 deliveries, which were divided into different menstrual groups, and the data on weeks of delivery, infant length, and infant weight is skewed, using the Mann-Whitney test, it was possible to deduce that the number of weeks of delivery, fetal length at birth, and weight of infants were not statistically significant between the two groups (see Table 4).

Table 4

Comparison of the postnatal related data

	≤4 days（n=21）	＞4 days（n=126）	Z	p
Weeks of delivery	39（36~39）	38（37~39）	-0.040	0.968
Infant length（cm）	2900（2600~3200）	3025（2480~3300）	-0.130	0.896
Infant weight（Kg）	49（46~50）	50（46~50）	-0.348	0.728

Discussion

Menstruation is the abscission of the endometrium with bleeding that accompanies the cyclic changes of the ovaries, and the establishment of regular menstruation is a sign of maturing reproductive function. The mechanisms of endometrial changes during menstruation mainly include the vasoconstriction hypothesis, the inflammatory response hypothesis and the tissue destruction hypothesis[7].Rhythmic contraction and diastole of the endothelial spiral arteries during the 24 hours before menstruation, resulting in ischemic necrosis and exfoliation of the distal vessel walls and tissues[8].Endometrial epithelial repair begins on day 2 of menstruation, and this phase is non-estrogen-dependent. On day 6, estrogen receptors and progesterone receptors in the endometrium are highly expressed, and the endometrium begins to enter an estrogen-dependent proliferative state[9].So the length of a woman's period may be influenced by many factors, including genetics, endocrine disorders, uterine and ovarian abnormalities, immune regulation, etc.As normal ovarian reserve women,is there a correlation between the length of menstrual periods with women's ovarian reserve function or IVF pregnancy outcome excluding uterine disease and genetics during the nearly 400 menstrual periods? Are there regulatory factors for scar-free endometrial repair that improve the uterine microenvironment and thus drive our research on endometrial tolerance and thin endometrium?

Currently, anti-Mtillerian hormone (AMH), basal estradiol (E2), follicle-stimulating hormone (FSH), basal luteinizing hormone (LH), and sinus follicle (AFC) are commonly used to assess ovarian function[10]. AMH is secreted by the granulosa cells of the sinus follicles and antral follicles of the ovary, which does not change with the menstrual cycle and has become a stable indicator for clinical testing in recent years[11].It is worth mentioning that although in patients with normal AMH, the low-response population still exists and is more likely to be ignored, so it has been suggested that basal FSH/LH may have a new predictive value for the assessment of Gn sensitivity and ovarian reserve function in IVF protocols.Kofinas Jason D[12]argued that as FSH/LH values increase, the patient's ovarian reserve function and IVF cycle success rates decrease accordingly.Liang X[13]believed that FSH/LH was significantly higher in patients who cancelled their IVF cycles compared to those who did not.In this retrospective study, it was found that patients with >4 days of menses had lower FSH/LH (2.60 (1.80-3.58) vs. 3.57 (2.58-8.33), $p<0.05$) and higher AMH (2.25 (1.18-3.83) vs. 1.73 (1.12-3.17), $p<0.05$) .We deduce that ovarian reserve function may be better in patients with >4 days of menstruation than in patients with ≤4 days of menstruation, as shown by the fact that in patients with ≤4 days of menstruation during in vitro fertilization, the initiation dose (bottles) (4 (3-4) vs 3 (2-4), $p<0.05$), total Gn dose(bottles) (36.00 (28.00-40.00) vs 32.00 (24.92-40.00), $p<0.05$) were significantly more than in

patients with >4 days of menstruation,While the number of eggs obtained (7.00 (5.00-10.00) vs. 8.00 (6.00-11.25), p<0.05), MII (7.00 (4.00-10.00) vs. 8.00 (5.00-11.00), p<0.05), 2PN (4.00 (3.00-6.00) vs. 5.00 (3.00-8.00), p < 0.05) lower than patients with periods >4 days.This finding is possibly related to the higher FSH/LH ratio found by Arat Ö, where patients obtained fewer mature oocytes[14].It has been suggested that elevated FSH/LH may reduce the success of the patient's final cycle[15].However, in this study, despite the statistical significance of clinical pregnancy, biochemical pregnancy, and non-pregnancy between the different groups (p=0.027 <0.05), due to the correlation coefficient r=0.115, it indicates that the association between the length of menstruation and pregnancy outcome is weak. And when it comes to complications in pregnant women, mode of delivery and postpartum fetal condition, no differences were found between the two groups for length of menstruation.

With the development of ART technology, although the improvement in the type of drugs used to promote ovulation has ensured that we have a significant number of eggs and good quality embryos, we are still lagging behind in improving the pregnancy rate significantly.Al Chami A believes that the key factors affecting the success of ART are 1/3 from the embryo and 2/3 from the endometrium[16].In recent years, research in the reproductive community has focused on endometrial receptivity, which refers to the ability of the endometrium to accept embryos, and on the search for the "window of implantation" (WOI), which refers to the optimal time to allow embryo implantation followed by pregnancy[17].It has been found that a decrease in endometrial blood flow may affect the growth of the uterine glandular epithelium, leading to a decrease in the expression of endothelial vascular endothelial growth factor in the endometrium[18].Reduced expression can lead to damage to the endometrial vascular system, decreasing the endometrial blood supply and causing endometrial growth restriction to form a thin endometrium, which is clinically manifested by shorter menstrual periods and reduced menstrual flow.It has been suggested that these factors that modulate the uterine glandular epithelium and small spiral arteries include endothelium-derived vasodilatory factors (endothelin ET, NO)[19], vascular endothelial growth factor (VEGF)[20], interferons, tumor necrosis factor[21], platelet-derived growth factor, and transforming growth factor[22].Another type of disease that presents as shorter periods and reduced menstrual flow is uterine adhesions. Some scholars used in vitro cell culture techniques to embryo the clone formation rate of stem cells from menstrual blood of patients with severe uterine adhesions and patients in the normal endometrial group, and found that there were significantly more endometrial stem cells in the normal control group than in patients with severe uterine adhesions[23].In this retrospective study, it can be found that patients with periods ≤4 days, patients with periods >4 days had thicker endometrial thickness at the day of transplantation (9.10 (7.60-10.10) vs. 10.80 (9.50-12.30), p < 0.05), while clinical pregnancies and biochemical pregnancies with periods >4 days were higher than those with periods ≤4 days (169 (38.2%) vs. 34 (33.0%)), (59(13.3%) vs 6(5.8%)), and non-pregnant patients with periods ≤4 days were higher than those with periods >4 days (63(61,.2%) vs 214(48.4%)), leading us to associate whether the length of periods is related to the number of endometrial stem cells.In recent years, some scholars have discovered that endometrial stem cells can be released into menstrual blood during menstruation as the endometrium collapses and sheds, allowing scientists to focus on menstrual blood-derived endometrial stem cells, which are stem cells with proliferative and multidirectional differentiation

potential isolated from menstrual blood. Some scholars have established a nude mice model of endometrial injury by mechanical method and demonstrated that endometrial stem cells from menstrual blood can survive intrauterine transplantation, while the pregnancy rate in the transplanted endometrial stem cell group was significantly higher than that in the control group[24-25].It is suggested that intrauterine implantation of transgenic endometrial stem cells may improve the embryonic implantation function of the damaged endometrium and thus increase the pregnancy rate. In a retrospective analysis of the mode of delivery and pregnancy complications, it was found that cesarean delivery was more common in both groups compared to vaginal delivery [15 (12.93%) vs 6 (19.35%), 101 (87.07%) vs 25 (80.65%), 0.364], although there was no statistical difference, probably because IVF pregnancy is more "precious". compared to this bias may be related to the fact that IVF women are more likely to deliver by cesarean section than women who deliver with normal pregnancy,the obstetricians may take the patient's wishes into account more. There were no statistical differences between the two groups for ectopic pregnancy, early miscarriage, late miscarriage, or the number of weeks of labor, infant length, or infant weight after follow-up delivery.

From this retrospective study, it can be deduced that the sensitivity of patients with <4 days of menstruation to pro-ovulatory drugs, the number of eggs obtained by pro-ovulation, the thickness of the endometrium on the transplantation day, and the pregnancy outcome (clinical pregnancy, biochemical pregnancy) are lower than those with ≥4 days of menstruation during IVF. However, the antagonist regimen used in this retrospective analysis, whether the results remain the same in other IVF regimens requires further accumulated clinical data analysis, and finally, the association between menstrual length and female endocrine needs to be explored and studied in more prospective clinical studies and at the basic molecular protein level.

Abbreviations

COS:controlled ovarian stimulation;IVF/ICSI: In Vitro Fertilization-Embryo Transfer/Intracytoplasmic sperm injection;FSH:follicle stimulating hormone;LH:luteinizing hormone;E2:oestradiol;AFC:antral follicle;COH:controlled ovarian hyperstimulation;AMH:anti-Müllerian hormone;BMI:body mass index;ICM:inner cell mass;TE:trophoblast;OPU:ovum pick-up;2PN:two pronuclear;WOI:window of implantation;VEGF:vascular endothelial growth factor;

Declarations

Acknowledgments

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Limitations subsection

This paper is a retrospective study. selection bias interfere with outcome.

Contributors

Yunzhu Lan: Contributed to study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript, and has full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Xingyu Sun and Ling Liu: Contributed to study concept and design, analysis and interpretation of data, study supervision.

Li Fu and Guiying Huang: Contributed to data analysis and editing of the manuscript, and provided expertise.

Xinjian Feng:reviewed and edited the manuscript

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from

the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Ethics Committee of Affiliated Hospital of Southwest Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Conflict of interest

The authors declare that they have no conflict of interest.

Consent to Publish

All authors in the study had signed the approved informed consent to allow

publication of anonymous data.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Abbreviations

COS
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Figures

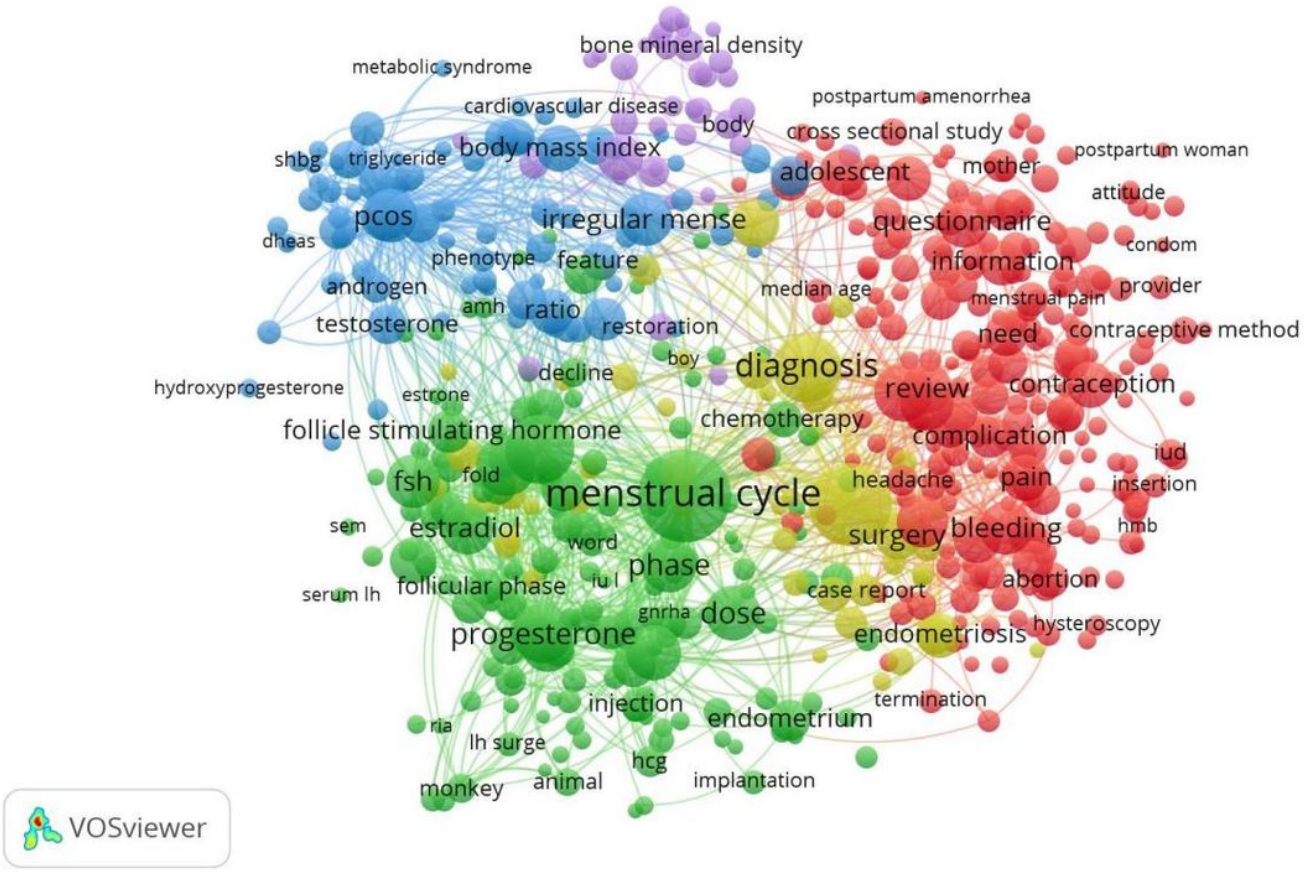

Figure 1

VOSviewer describes the distribution of relevant literature on "menses"

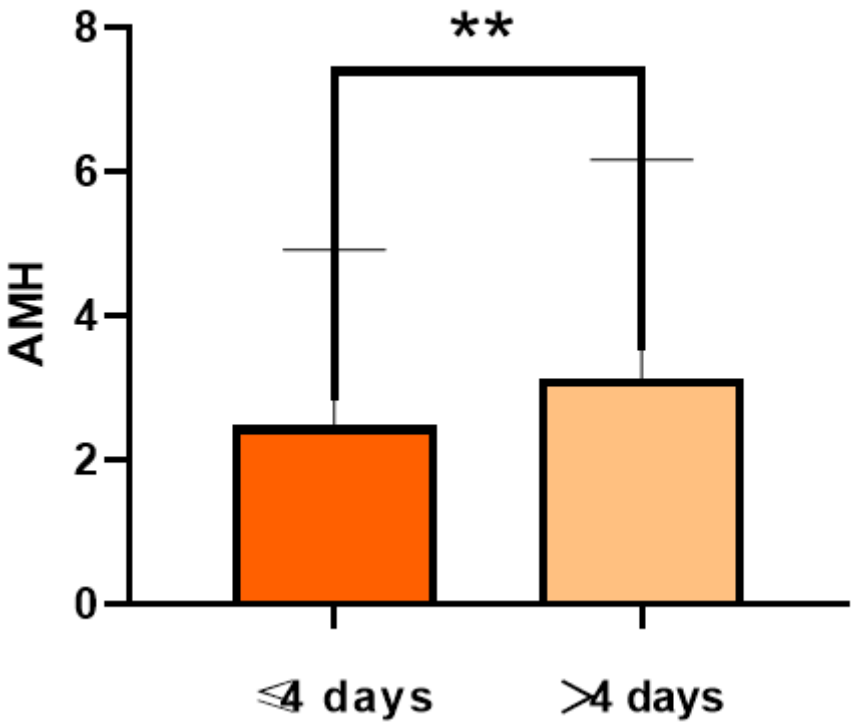

Figure 2

AMH histogram

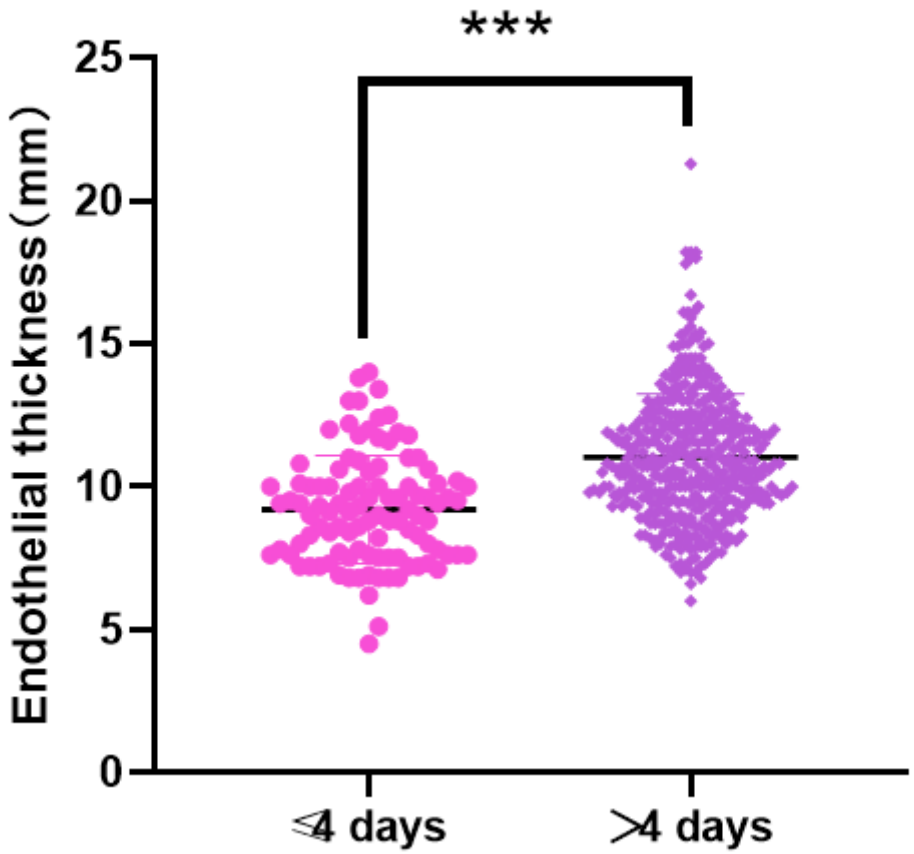

Figure 3

The scatter plot of endothelial thickness at transplantation day

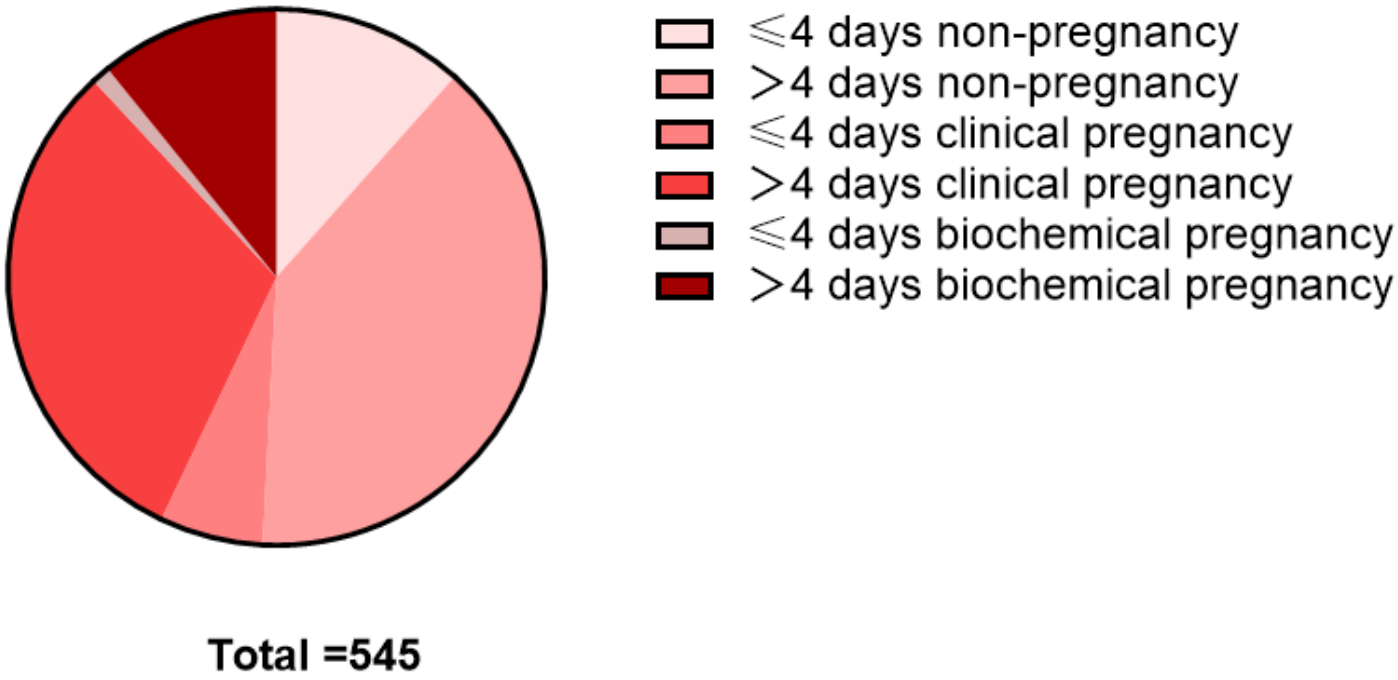

Figure 4

pie charts of pregnancy outcomes

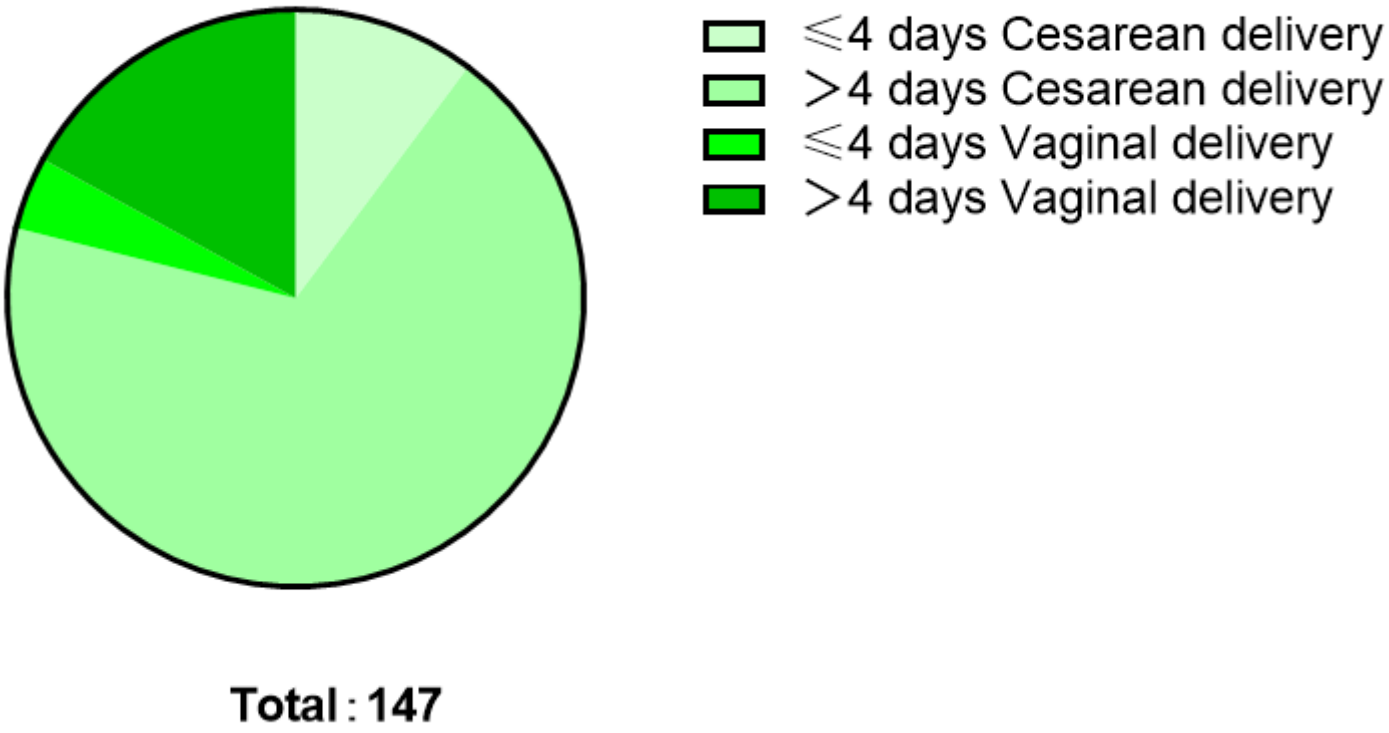

Figure 5

The mode of delivery

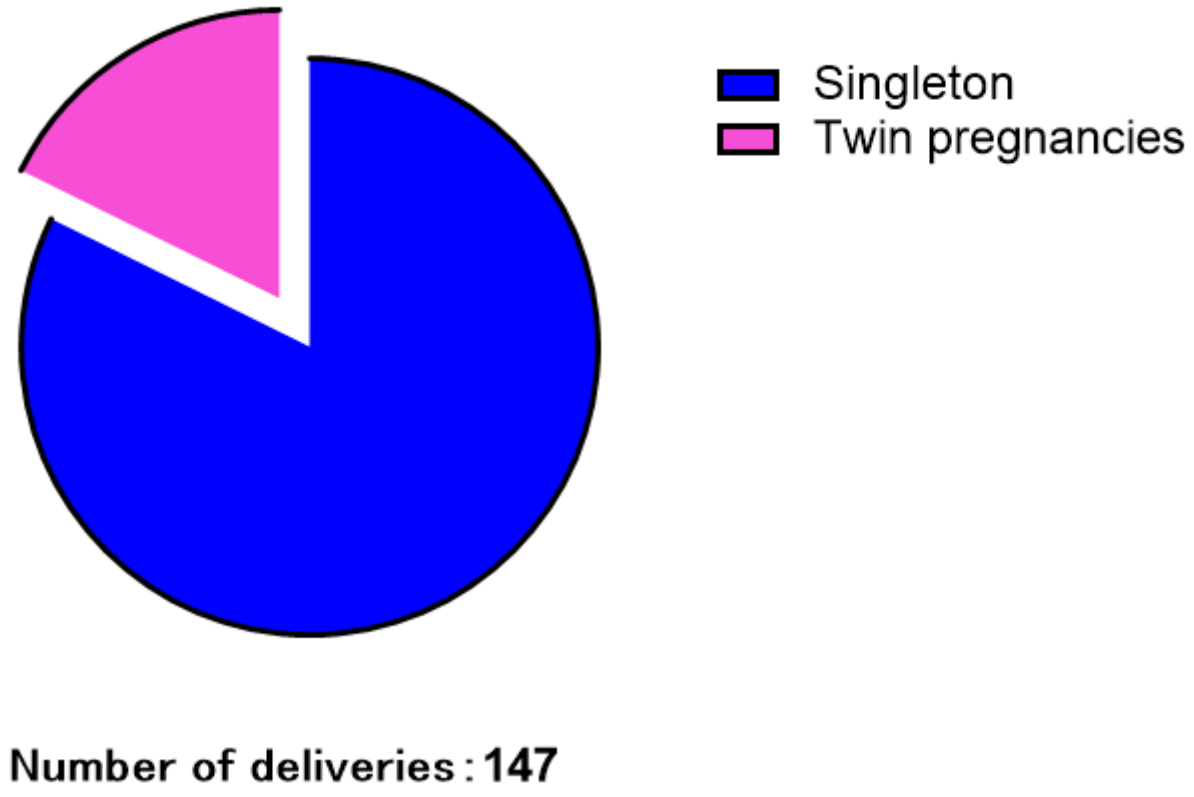

Figure 6

Number of deliveries