Patients with IVF complicated by moderate-to-critical OHSS experience increased thrombosis,GDM and neonatal NICU admission but slightly shorter gestation compared with matched IVF counterparts: A retrospective Chinese cohort study

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Research

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Abstract

Background : Ovarian hyperstimulation syndrome (OHSS) is a common disease during controlled ovarian hyperstimulation treatment. However, the obstetrics and neonatal outcomes of these group of patients are barely known. The aim of this study was to explore the effects of late moderate-to-critical ovarian hyperstimulation syndrome (OHSS) on obstetric and neonatal outcomes. Methods: This is a prospective observational study including 17,537 patients after IVF/ICSI-fresh embryo transfer (ET) from June 2012 to July 2016, after meeting the inclusion and exclusion criteria, of whom 7064 eligible patients were diagnosed with clinical pregnancy. Finally, 6356 patients were allocated to the control group, and 385 patients who were hospitalized and treated at the center for late moderate-to-critical OHSS were allocated to the OHSS group. Results: The live birth delivery rate did not significantly differ between the OHSS and the macthed control groups, and the incidence rates of the obstetric complications venous thrombosis (VT), gestational diabetes mellitus (GDM), neonatal complications and the numbers of neonates admitted to the NICU were significantly higher in the OHSS group than that in the macthed control group. The duration of gestation was significantly higher in the macthed control group than that in the OHSS group. Conclusions: Late moderate-to-critical OHSS could reduce gestational time, increase obstetric complications and neonatal complications. However, the incidence rates of live birth rate, premature delivery, miscarriage, early abortion, hypertensive disorder of pregnancy (HDP), Placenta previa (PP), Intrahepatic cholestasis of pregnancy (ICP), average neonatal weight and LBW did not statistically significant difference between the two groups.

Introduction

The widespread use of assisted reproductive technology (ART) in the clinic to enhance oocyte number has increased the prevalence of ovarian hyperstimulation syndrome (OHSS) [1, 2]. The etiopathogenesis of OHSS remains unclear, but hCG, VEGF, angiotensin, and interleukin seem to be the key players in OHSS patients. These factors increase capillary permeability and cause blood volume reduction, blood concentration, liver function damage, kidney function damage, water and electrolyte disorders, thrombosis, acute respiratory distress syndrome and other clinical manifestations, and the condition can be life-threatening[3-5]. Clinical studies indicate that the incidence of moderate-to-severe OHSS is approximately 2-3%. The clinical symptoms of OHSS are highly variable, difficult to precisely classify, and lacking in uniform standards, making accurate clinical data collection and unified classification difficult.

Recently, numerous reports on the prevention and treatment of OHSS have been published. However, reports on the consequences of the pregnancy outcomes of OHSS are poorly understood and remain controversial, which may be because the impact of late OHSS on pregnancy outcomes is difficult to predict [6-10]. Earlier studies have demonstrated that pregnancy and abortion rates increase significantly among OHSS patients and that these patients are more likely to develop adverse pregnancy outcomes such as abortion, growth restriction, hypertensive disorder of pregnancy (HDP), gestational diabetes mellitus (GDM) and low neonatal birth weight (LBW) [1, 11-17]. In addition, one study reported that the hospitalization of OHSS patients who underwent IVF was not conducive to pregnancy or continued pregnancy [18]. The aim of this study was to investigate the effects of late moderate-to-critical OHSS on pregnancy and neonatal outcomes.

Materials And Methods

This prospective observational study was approved by the institutional Review Board of the First Affiliated Hospital of Zhengzhou University and the Institutional ethics committee Review Board of the First Affiliated Hospital of Zhengzhou University, Zhengzhou University (Scientific research-2019-LW-046). This study was retrospectively registered on May 26th, 2017 (ChiCTR-1800014655).

Exclusion criteria included the following: PGT, donor sperm and donor oocyte, female age > 40 years, clinical data missing. Firstly, a total of 17,537 patients from June 2012 to July 2016 were evaluated. Then, 385 OHSS patients and 6356 non-OHSS patients were allocated eventually. Baseline characteristics including maternal age, infertility duration, BMI, basal FSH, basal LH, AFC, infertility cause, estradiol level on the hCG trigger day (pg/ml), and the number of oocytes retrieved from follicles with diameters ≥12 mm were collected. The primary outcomes of our study were pregnancy outcomes, obstetric and neonatal complications, live birth delivery rate, miscarriage rate, gestational age at birth (weeks) and neonatal birth weight.

The classification criteria for OHSS were as follows: early-onset OHSS indicated the occurrence of OHSS no later than 9 days after the hCG injection, and late OHSS indicated the occurrence of OHSS generally no earlier than 10 days after the hCG injection [5, 15].

The Classifification of OHSS symptoms were as follows: Mild: Abdominal distension/discomfort, Mild nausea/vomiting, Mild dyspnea, Diarrhea, Enlarged ovaries, No important alterations. Moderate: Mild features, Ultrasonographic evidence of ascites, Hemoconcentration (Hct >41%), Elevated WBC (>15,000 mL). Severe: Mild and moderate features, Clinical evidence of ascites, Hydrothorax, Severe dyspnea, Oliguria/anuria, Intractable nausea/vomiting, Severe hemoconcentration (Hct >55%), WBC >25,000 mL, CrCl <50 mL/min, Cr >1.6 mg/dL, Na+ <135 mEq/L, K+>5 mEq/L, Elevated liver enzymes. Critical: Low blood/central venous pressure, Pleural effusion, Rapid weight gain (>1 kg in

24 h), Syncope, Severe abdominal pain, Venous thrombosis, Anuria/acute renal failure, Arrhythmia, Thromboembolism, Pericardial effusion, Massive hydrothorax, Arterial thrombosis, Adult respiratory distress syndrome,Sepsis, Worsening of fifindings.

Statistical analysis

Propensity score matching was used to further validate the logistic regression analysis results. For the propensity score analysis, we performed one-to-four matching without replacement on the nearest propensity scores of the OHSS and control groups [19-24].

Categorical data are represented as frequencies and percentages, and the differences in these measures between the study groups were assessed by chi-square analysis with Fisher's exact test for expected frequencies of less than 5. Continuous data are expressed as the means ± standard deviations (SD) using IBM SPSS Statistics Version 22. Significance testing was 2-sided, and P<0.05 was considered statistically significant.

Results

After meeting the inclusion and exclusion criteria, 6356 patients were allocated to the control group, and 385 (3.03%) patients who were hospitalized and treated at the center with late moderate-to-critical OHSS were allocated to the OHSS group. The patients were then grouped by propensity score matching, as shown in the flow chart in Figure 1.

Factors associated with OHSS

The patients in our center were characterized by the following OHSS risk factors: young age; low BMI; ovulation disorders or PCOS; low basal FSH level; higher E_2 level on hCG trigger day; and follicles ≥12 mm on the trigger day of final oocyte maturation (Table 1).

Study patients

Basic patient parameters in the two groups are presented in Table 1. Propensity score matching analysis was performed with matching on multiple maternal baseline characteristics (one-to-four), and the analysis yielded 1540 non-OHSS patients. The baseline patient characteristics and the number of multiple gestation pregnancies were similar between the two study groups (Table 1).

Pregnancy and neonatal outcomes

The binary logistic regression analysis was first used to compare the perinatal outcomes of the OHSS group and the unmatched control group. The pregnancy and neonatal outcomes are detailed in Table 2.

Before matching, several parameters were different between patients in OHSS group and controls. However, after propensity score matching, compare the perinatal outcomes of the OHSS group and the matched control group. The live birth delivery rate of singleton and preterm delivery rate were not significantly different between the two groups. The incidence rate of obstetric complications of concern was significantly higher in the OHSS group than that in the matched control group (7.0% vs. 3.2%; P=0.001). Moreover, the GDM and venous thrombosis (VT) rates were higher in the OHSS group than those in the matched control group (1.8% vs. 0.6%; P=0.017; 0.5% vs. 0%; P=0.04).

The incidence rates of neonatal complications and the numbers of neonates admitted to the NICU were significantly higher in the OHSS group than that in the macthed control group (3.6% vs. 2.1%; P=0.045; 3.2% vs. 1.7%; P=0.034). The duration of gestation was significantly higher in the matched non-OHSS group than that in the OHSS group (38.7±2.1 vs. 38.0±2.2;P□0.001). However, no significant between-group differences were evident for average neonatal weight (g) or LBW (2800.7±588.6 vs. 2853.6±659.6;P=0.081; 25.5% vs. 27.1%;P=0.441).

Characteristics of the moderate to critical OHSS patients

The OHSS group comprised 385 patients (83 moderate OHSS; 289 severe OHSS; 13 critical OHSS), with an average length of hospital stay of 12.7±6.9 days.

The OHSS group included 302 (78.4%) patients who suffered from severe or critical OHSS. Upon admission, patients were hospitalized longer and the percentage of patients receiving puncture surgery was higher in the severe-to-critical group than the moderate group (9.3±4.7 vs. 13.8±7.2, (P<0.001), 16.9% vs. 44.0%, (P<0.001)), and the HCT and WBC values were higher in the severe-to-critical group than those in the moderate group (42.0±4.1 vs. 44.9±5.7 (P<0.001), 14.0±4.4 vs. 15.4±4.8 (P=0.012)) as shown in Table 3. Compared with the matched control group with the same baseline characteristics, the incidence rates of miscarriages, live birth delivery, premature delivery and LBW were not significant difference between groups. The incidence rate of obstetric complications was significantly higher in the severe and critical OHSS group than those in the matched control group, however those were not significant difference between moderate group and severe-to-critical group, moderate group and matched control group. The incidence rate of neonatal complications was significantly higher in the moderate

group than those in the matched control group, however those were not significant difference between moderate group and severe-to-critical group, severe-to-critical group and matched control group. The average neonatal weight was significantly higher in severe-to-critical group and matched control group than moderate group. The duration of gestation was significantly higher in matched control group than that in severe-to-critical group and moderate group.

Discussion

The occurrence of OHSS-associated hospitalizations increases the economic burden and affects patient mental wellbeing after IVF-ET [25]. However, different races, different regions, hospitals or research methods may affect the impact of OHSS on pregnancy outcomes, such as baseline characteristics or severity of OHSS confounders patient may affect the interpretation of results during the course of clinical research. The pregnancy outcomes of pregnancies effected by OHSS has not yet been investigated thoroughly and further studies are needed[8, 12]. The results of our data in the OHSS group and the unmatched control group showed that the rates of multiple live birth delivery and LBW were significantly higher in the OHSS group.

After eliminating the impacts of multiple pregnancies and nine baseline characteristics on perinatal complications using propensity score matching. Furthermore, the results of our data in the OHSS group and the matched control group showed that the incidence rates of obstetric complications and neonatal complications were significantly higher in the OHSS group than those in the control group, including the incidence of GDM, VT, congenital disorders and neonatal NICU hospitalization. No significant between-group differences with respect to the rates of preterm delivery, miscarriage, early miscarriage.

A previous case-control study reported that the hospitalization duration of OHSS patients was positively related to the increase in the rate of miscarriage, and OHSS hospitalization was not conducive to pregnancy or continued pregnancy in patients who underwent IVF [18]. All the patients in two groups were included in the clinical pregnancy, the abortion rate of the unmatched control group was higher than the OHSS group, but there was no statistical difference (12.2% vs. 15.4%, P=0.098). There was no difference in the abortion rate between the two groups after matching. 12.2% vs. 13.6%, P=0.481). It is possible that the occurrence and treatment of OHSS does not affect the abortion rate.

In our study, obstetric complications were significantly higher in the OHSS group than those in the control group, but the incidence rates of PP, HDP, and ICP were not increased after OHSS, and the rates were consistent with previously reported post-IVF rates [25, 26]. Our results were similar to several previous reports that assessed this outcome [12, 14]. A previous symposium by Raziel et al. in 2009 and a previous case-control study indicated that the pregnancy rate is increased in OHSS patients and that the incidence rates of multiple pregnancy, GDM, premature birth, and LBW infants are significantly higher in OHSS [8]. We observed thrombosis only appear in the OHSS group. These results are somewhat inconsistent with previous findings because the obstetric complications examined here were not evaluated in previous studies[8, 13, 14].

A previous study model suggested that outpatient treatment of moderate-to-severe OHSS with early intervention using paracentesis is the most cost-effective management option [27]. Furthermore, a previous study indicated that repeated abdominal paracentesis has no adverse effects on pregnancy outcomes in severe OHSS[28]. Patients who undergo paracentesis are not at risk for obstetric complications. The observed increased prevalence of obstetric complications (11.6%) in our study is consistent with findings from previous studies [29].

At admission, HCT and WBC values were positively correlated with the degree of OHSS and patient symptoms and were associated with an increased rate of surgical treatment. The number of hospital stays in the severe-critical group increased compared with that in the moderate group, and obstetric complications decreased; however, neonatal complications increased, as shown in Table 3. The severity of OHSS increased the incidence rates of obstetrical complications and preterm delivery but had no effect on neonatal complications.

Conclusions

After eliminating the effects of confounding factors, late moderate to severe OHSS could reduce gestational time, increase obstetric complications and neonatal complications, including the incidence of GDM, VT, congenital disorders and neonatal NICU hospitalization. However, the incidence rates of live birth rate, premature delivery, miscarriage, early abortion, HDP, PP, ICP, average neonatal weight and LBW did not statistically significant difference between the two groups.

List Of Abbreviations

IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; BMI: body mass index; hCG: human chorionic gonadotropin; HDP: pregnancy-induced hypertension; GDM: gestational diabetes mellitus; LBW: low birth weight; OHSS: ovarian hyperstimulation syndrome.

Declarations

Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Ethical approval and consent to participate

The study has received approval and was carried out in accordance with the approved guidelines from the Zhengzhou University Research Ethics Board.

Consent for publication

Not applicable

Availability of data and material

All data supporting the conclusion of this article are included.

Competing interests

The authors declare that they have no competing interest.

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Author contributions

LL.H and R.X contributed to the study design, data analysis and manuscript preparation. MY. W handled patient recruitment and data collection. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of the patients at baseline and outcomes of controlled ovarian hyperstimulation.

Baseline characteristics	OHSS group (n=385)	Control group			
		Unmatched (n=6356)	P value	Matched 1:4 (n=1540)	P value
Age (years), mean ±SD	29.3±3.8	30.3±4.3	<0.001	29.4±4.0	0.585
BMI (kg/m^2)	21.8±2.7	22.5±3.0	<0.001	21.8±2.7	0.997
Duration of infertility (years)	3.8±2.4	4.2±3.0	0.002	3.8±2.6	0.964
Baseline FSH (mIU/ml)	6.5±1.7	7.1±2.2	<0.001	6.5±1.8	0.876
Baseline LH (mIU/ml)	6.0±4.3	5.4±3.3	0.005	6.0±4.0	0.939
AFC	14.7±5.8	12.8±6.0	<0.001	14.5±6.4	0.588
Indications for IVF					
Unexplained factors (%)	10 (2.6)	320 (5.0)	0.031	42 (2.7)	0.888
Anovulatory disorders (includes PCOS)	67 (17.4)	563 (4.9)	<0.001	216 (14.0)	0.094
Tubal factors	157 (40.8)	2923 (46.0)	0.046	670 (43.5)	0.334
Endometriosis-associated	7 (1.8)	137 (2.2)	0.657	25 (1.6)	0.789
Male factors	111 (28.8)	2060 (32.4)	0.144	449 (29.2)	0.900
Pelvic inflammatory disease	3 (0.8)	56 (0.9)	1	13 (0.8)	1.000
Multiple factors	33 (8.6)	605 (9.5)	0.538	138 (9.0)	0.810
E_2 level on hCG trigger day (pg/ml)	4484.9±1905.8	4098.5±2715.2	<0.001	4521.6±4030.0	0.795
No. of oocytes retrieved	12.2±2.9	10.5±3.8	<0.001	12.2±4.0	0.906
Multiple gestations, no. (%)	179 (46.5)	1719 (27.1)	<0.001	725 (47.0)	0.837

Note: Data are expressed as n (%) unless otherwise indicated. Plus-minus values are the mean±SD; SD: Standard deviation. Statistically significant at P<0.05. OHSS, Ovarian hyperstimulation syndrome; IVF, In vitro fertilization; AFC, Antral follicle count; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; hCG, Human chorionic gonadotropin; BMI, Body mass index (the body mass index is the weight in kilograms divided by the square of the height in meters); PCOS, Polycystic ovary syndrome (polycystic ovaries were defined as the presence of an antral follicle count of 12 or more or a volume of more than 10 cm^3 in at least one ovary); Multiple factors, Infertility due to more than one infertility factor; Multiple gestations, diagnosis based on ultrasound during early pregnancy.

Table 2. Pregnancy and neonatal outcomes of Logistic and Propensity score matching.

Outcomes	OHSS group (n=385)	Binary logistic regression analysis		Propensity score matching	
		Unmatched (n=6356)	P value	Matched 1:4 (n=1540)	P value
Live birth delivery rate, no. (%)	338/385 (87.8)	5380/6356 (84.6)	0.164	1331/1540 (86.4)	0.481
Singleton, no. (%)	174/338 (51.5)	3913/5380 (72.7)	<0.001	721/1331 (54.2)	0.376
Multiple, no. (%)	164/338 (48.5)	1467/5380 (27.3)	<0.001	610/1331 (45.8)	0.376
Preterm delivery, no. (%)	67/338 (19.8)	1456/5380 (27.1)	<0.001	262/1331 (19.7)	0.955
Miscarriages, no. (%)	47/385 (12.2)	976/6356 (15.4)	0.164	209/1540 (13.6)	0.481
Early miscarriages, no. (%)	23/385 (6.0)	607/6356 (9.6)	0.160	137/1540 (8.9)	0.063
Obstetric complications, no. (%)	27/385 (7.0)	414/6356 (6.5)	0.700	49/1540 (3.2)	0.001
PP, no. (%)	3/385 (0.8)	35/6356 (0.6)	0.404	5/1540 (0.3)	0.215
GDM, no. (%)	7/385 (1.8)	82/6356 (1.3)	0.178	9/1540 (0.6)	0.017
PIH, no. (%)	12/385 (3.1)	137/6356 (2.2)	0.117	34/1540 (2.2)	0.184
ICP, no. (%)	2/385 (0.5)	7/6356 (0.1)	0.056	1/1540 (0.1)	0.104
VT, no. (%)	2/385 (0.5)	0	<0.001	0	0.040
Duration of gestation (weeks) (mean+SD)	38.0±2.2	38.7±2.0	0.020	38.7±2.1	<0.001
Neonatal births	503	6855		1946	
Neonatal complications, no. (%)	18/503 (3.6)	193/6855 (2.8)	0.322	40/1946 (2.1)	0.045
NICU, no. (%)	16/503 (3.2)	143/6855 (2.1)	0.103	33/1946 (1.7)	0.034
Congenital diseases, no. (%)	2/503 (0.4)	15/6855 (0.2)	0.420	1/1946 (0.1)	0.048
Average neonatal weight (g) (mean+SD)	2800.7±588.6	3040.0±655.3	<0.001	2853.6±659.6	0.081
LBW, no. (%)	128/503 (25.5)	1228/6855 (17.9)	<0.001	528/1946 (27.1)	0.441

Note: Data are n (%) unless otherwise indicated. Plus-minus values are the mean±SD; SD, Standard deviation. Statistically significant ($P<0.05$). OR, Odds ratio.

Live birth delivery rate; the number of deliveries that resulted in at least one live birth, expressed per 100 cycle attempts. the denominator in our study is the number of pregnancies who were diagnosed with clinical pregnancy after IVF/ICSI- fresh ET.

Premature delivery was defined as birth before 37 completed weeks and after 28 completed weeks of pregnancy.

Miscarriage included early- and late-term miscarriages. Early miscarriages occurred before 12 gestational weeks, and late-term miscarriages occurred between 13 and 28 gestational weeks.

Obstetric complications; PP, Placenta previa; GDM, Gestational diabetes mellitus; PROM, Premature rupture of the fetal membranes; PIH, pregnancy-induced hypertension; ICP, Intrahepatic cholestasis of pregnancy; VT, Venous thrombosis.

Neonatal complications included prematurity, extremely low birth weight, perinatal asphyxia, major birth defects, sepsis, neonatal jaundice, and infant respiratory distress syndrome due to immaturity of the lungs.

NICU, neonatal intensive care unit, which concentrates on the care of premature babies and sick newborns, due to extreme low birth weight (LBW), perinatal asphyxia, major birth defects, sepsis, neonatal jaundice, and infant respiratory distress syndrome due to immaturity of the lungs and other complications.

Other neonatal complications: One neonatal death occurred in the NICU, and two congenital diseases occurred in the OHSS group. In the matched non-OHSS group, one death occurred within one year after birth, and one congenital disease, one chromosomal abnormality and five congenital diseases were present.

LBW, Low birth weight (birth weight <2500 g).

Threatened abortion refers to a small amount of vaginal bleeding, often dark red or bloody leukorrhea and accompanying paroxysmal abdominal pain or lower back pain in the absence of pregnancy discharge at <28 weeks of pregnancy.

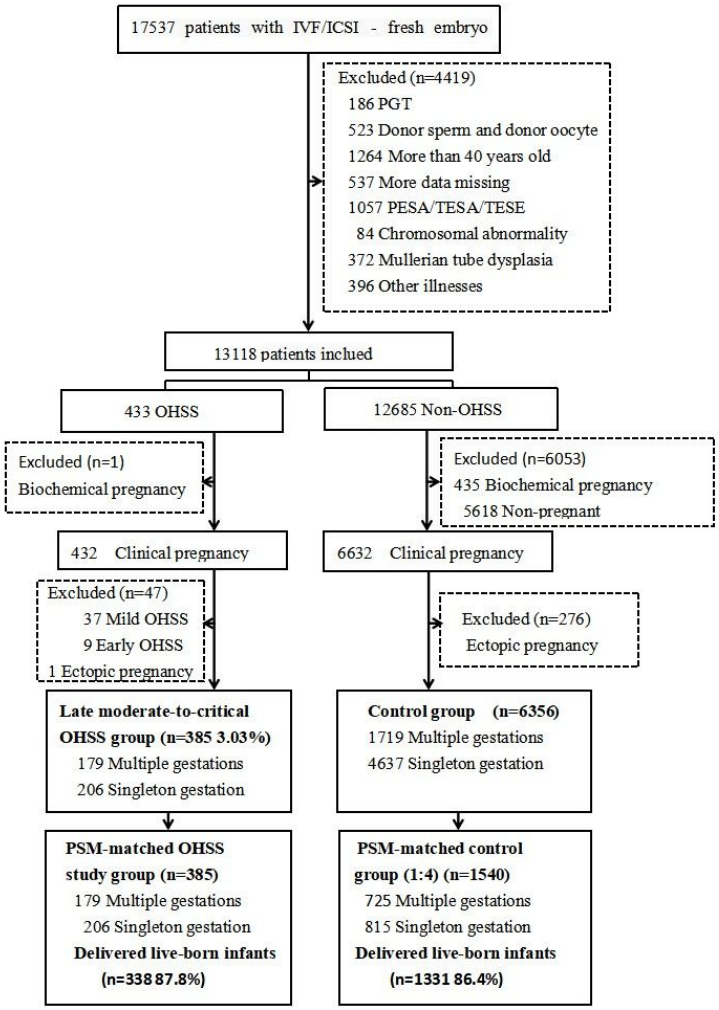
Table3. The characteristics of the OHSS group patients.

Characteristic	Moderate group (n=83)	Severe-to-critical group (n=302)	Matched control group 1:4 (n=1540)	P1 value1-2	P2 value1-3	P3 value2-3
E_2 level on hCG trigger day (pg/ml)	4739.0±1754.6	4415.2±1935.7	/	0.171	/	/
Hospital days (days)	9.3±4.7	13.8±7.2	/	<0.001	/	/
DT (days)	14.0+3.3	13.1+4.7	/	0.136	/	/
HCT (%)	42.0±4.1	44.9±5.7	/	<0.001	/	/
WBC (×109)	14.0±4.4	15.4±4.8	/	0.012	/	/
Albumin (g/L)	37.0±4.2	36.7±5.0	/	0.574	/	/
Surgical treatment, no. (%)	14/83 (16.9)	133/303 (44.0)	/	<0.001	/	/
Miscarriages, no. (%)	9/83 (10.8)	38/302 (12.6)	209/1540 (13.6)	0.668	0.478	0.645
Live birth delivery rate, no.(%)	74/83 (89.2)	264/302 (87.4)	1331/1540 (86.4)	0.668	0.478	0.645
Obstetric complications	6/83 (7.2)	21/302 (7.0)	49/1540 (3.2)	0.931	0.058	0.002
Neonatal complications	6/108 (5.6)	12/395 (3.0)	40/1946 (2.1)	0.240	0.031	0.227
Premature delivery	15/74 (20.3)	52/264 (19.7)	262/1331 (19.7)	0.913	0.902	0.996
Average neonatal weight (g)	2698.8±666.2	2828.6±563.2	2853.6±659.6	0.042	0.018	0.436
Singletons	41 /74 (55.4)	133/264 (44.0)	721/1331 (54.2)	0.444	0.835	0.259
Multiples	33/74 (44.6)	131/264 (49.6)	610/1331 (45.8)	0.444	0.835	0.259
Duration of gestation (weeks)	37.8±2.8	38.1±2.0	38.7±2.1	0.435	<0.001	0.001
LBW, no.(%)	30/108 (27.8)	98/395 (24.8)	528/1946 (27.1)	0.530	0.883	0.342

Note: Data are n (%) unless otherwise indicated. Plus-minus values are the mean±SD; SD: Standard deviation. Statistically significant at P<0.05.
Statistical analysis of baseline data in the above groups revealed no difference, and the results are not shown.
P1 value was Moderate group vs. Severe-to-critical group,
DT, Days after transplantation; OHSS patients were hospitalized for several days after transplantation.
HCT, Red blood cell-specific volume. Normal range of values: 37-43%; pregnant: <35%.
WBC, White blood cell count. Normal range of values: 15-22×10^9/l, pregnant: 6-20×10^9/l.

Figures

Fig.1. Study Enrollment and Outcomes.



Clinical pregnancy: A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. In addition to intra-uterine pregnancy, it includes a clinically documented ectopic pregnancy. PSM: Propensity score matching.

Figure 1

Study enrollment and outcomes.