Perinatal outcomes in women with in vitro fertilization pregnancies hospitalized for late moderate-to-critical ovarian hyperstimulation syndrome: A prospective observational study

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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 and neonatal complication rates did not significantly differ between the OHSS and control groups, and the incidence rates of the obstetric complications venous thrombosis (VT) and gestational diabetes mellitus (GDM) were significantly higher 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, PIH, PP, 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, pregnancy-induced hypertension (PIH), 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: PGD/PGS, 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. 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].

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 Fig. 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 E₂ level on hCG trigger day; and follicles ≥ 12 mm on the trigger day of final oocyte maturation (Table 1).
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/m²)              | 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   |
| E2 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 cm³ in at least one ovary); Multiple factors, infertility due to more than one infertility factor; Multiple gestations, diagnosis based on ultrasound during early pregnancy.

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.
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)       | 0.164                               | 1331/1540 (86.4)          | 0.481                     |
| Singleton, no. (%)            | 174/385 (51.5)       | [0.001]                             | 721/1331 (54.2)           | 0.376                     |
| Multiple, no. (%)             | 164/385 (48.5)       | [0.001]                             | 610/1331 (45.8)           | 0.376                     |
| Preterm delivery, no. (%)     | 67/385 (19.8)        | [0.001]                             | 262/1331 (19.7)           | 0.955                     |
| Miscarriages, no. (%)         | 47/385 (12.2)        | 0.164                               | 209/1540 (13.6)           | 0.481                     |
| Early miscarriages, no. (%)   | 23/385 (6.0)         | 0.160                               | 137/1540 (8.9)            | 0.063                     |
| Obstetric complications, no. (%)| 27/385 (7.0)         | 0.700                               | 49/1540 (3.2)             | 0.001                     |
| PP, no. (%)                   | 3/385 (0.8)          | 0.404                               | 5/1540 (0.3)              | 0.215                     |
| GDM, no. (%)                  | 7/385 (1.8)          | 0.178                               | 9/1540 (0.6)              | 0.017                     |
| PIH, no. (%)                  | 12/385 (3.1)         | 0.117                               | 34/1540 (2.2)             | 0.184                     |
| ICP, no. (%)                  | 2/385 (0.5)          | 0.056                               | 1/1540 (0.1)              | 0.104                     |
| VT, no. (%)                   | 2/385 (0.5)          | [0.001]                             | 0                        | 0.040                     |
| Duration of gestation (weeks) | 38.0 ± 2.2           | 0.020                               | 38.4 ± 2.2                | 0.011                     |
| NICU, no. (%)                 | 18/503 (3.6)         | 0.322                               | 40/1946 (2.1)             | 0.045                     |
| NICU, no. (%)                 | 18/503 (3.6)         | 0.322                               | 40/1946 (2.1)             | 0.045                     |
| Congenital diseases, no. (%)  | 2/503 (0.4)          | 0.420                               | 1/1946 (0.1)              | 0.048                     |
| Average neonatal weight (g)   | 2800.7 ± 588.6       | [0.001]                             | 2853.6 ± 659.6            | 0.081                     |
| LBW, no. (%)                  | 128/503 (25.5)       | [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.
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 matched 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 (38.4 ± 2.2 vs. 38.0 ± 2.2; P = 0.011). 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 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 and critical OHSS. The mean hospitalization duration, obstetric complications and average newborn weight were significantly higher in the severe and critical OHSS group than those in the moderate OHSS group (9.3 ± 4.7 vs. 13.8 ± 7.2 (P < 0.001), 5 (6.0) vs. 46 (20.1) (P = 0.028); 2698.8 ± 666.2 vs. 2828.6 ± 563 (P = 0.042)). However, the preterm delivery rate was significantly higher in the moderate OHSS group than that in the severe and critical OHSS group (15 20.3% vs. 12 5.4% (P < 0.001)). Upon admission, the HCT and WBC values
were higher in the moderate group than those in the control 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.

Table 3
The characteristics of the OHSS group patients.

| Characteristic                          | Moderate group (n = 83) | Severe-to-critical group (n = 302) | P value   |
|-----------------------------------------|------------------------|-----------------------------------|-----------|
| Maximal E2 (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     |
| Miscarriages, no. (%)                   | 9 (10.8)               | 38 (12.6)                         | 0.668     |
| Live birth delivery rate, no. (%)       | 74 (89.2)              | 264 (87.4)                        | 0.668     |
| Obstetric complications                 | 5 (6.0)                | 46 (20.1)                         | 0.028     |
| Neonatal complications                  | 3 (4.1)                | 9 (3.4)                           | 1.000     |
| Premature delivery                      | 15 (18.1)              | 12 (5.4)                          | < 0.001   |
| Average birth weight (g)                | 2698.8 ± 666.2         | 2828.6 ± 563.2                    | 0.042     |
| Surgical treatment, no. (%)             | 14 (16.9)              | 133 (44.0)                        | < 0.001   |
| Singletons                              | 41 (49.4)              | 133 (44.0)                        | 0.444     |
| Multiples                               | 33 (39.8)              | 131 (43.4)                        | 0.555     |
| Duration of gestation (weeks)           | 37.8 ± 2.8             | 38.1 ± 2.0                        | 0.246     |
| 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     |
| LBW, no. (%)                            | 30 (27.8)              | 98 (24.8)                         | 0.530     |

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.

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 × 10⁹/l; pregnant: 6–20 × 10⁹/l.

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].

We found the incidence of OHSS was significantly higher in the multiple than that in the singleton pregnancy, which is consistent with previous findings [14]. 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, PIH, 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, PIH, PP, ICP, average neonatal weight and LBW did not statistically significant difference between the two groups.

Abbreviations

IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; BMI: body mass index;
hCG: human chorionic gonadotropin; PIH: 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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**Declaration**

**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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Figures
Figure 1

Study enrollment and outcomes.
