Pregnancy Outcomes of In Vitro Fertilization with or without Ovarian Hyperstimulation Syndrome: A Retrospective Cohort Study in Chinese Patients

Xuan Jiang, Cheng-Yan Deng, Zheng-Yi Sun, Wei-Lin Chen, Han-Bi Wang, Yuan-Zheng Zhou, Li Jin
Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China

Background: The effect of ovarian hyperstimulation syndrome (OHSS) on pregnancy outcomes of in vitro fertilization (IVF) patients is still ambiguous. This study aimed to analyze pregnancy outcomes of IVF with or without OHSS in Chinese patients.

Methods: A retrospective cohort study was undertaken to compare pregnancy outcomes between 190 women with OHSS and 197 women without OHSS. We examined the rates of clinical pregnancy, multiple pregnancies, miscarriage, live birth, preterm delivery, preterm birth before 34 weeks’ gestation, cesarean delivery, low birth weight (LBW), and small-for-gestational age (SGA) between the two groups. Odds ratios (ORs) and 95% confidence intervals (CIs) of measure of clinical pregnancy were also analyzed.

Results: The clinical pregnancy rate of OHSS patients was significantly higher than that of non-OHSS patients (91.8% vs. 43.5%, P < 0.001). After controlling for drug protocol and causes of infertility, the adjusted ORs of moderate OHSS and severe/critical OHSS for clinical pregnancy were 4.65 (95% CI, 1.86–11.61) and 5.83 (95% CI, 3.45–9.86), respectively. There were no significant differences in rates of multiple pregnancy (4.0% vs. 3.7%) and miscarriage (16.1% vs. 17.5%) between the two groups. With regard to ongoing clinical pregnancy, we also found no significant differences in the rates of live birth (82.1% vs. 78.8%), preterm delivery (20.9% vs. 17.5%), preterm birth before 34 weeks’ gestation (8.6% vs. 7.9%), cesarean delivery (84.9% vs. 66.3%), LBW (30.2% vs. 23.5%), and SGA (21.9% vs. 17.6%) between the two groups.

Conclusion: OHSS, which occurs in the luteal phase or early pregnancy in IVF patients and represents abnormal transient hemodynamics, does not exert any obvious adverse effect on the subsequent pregnancy.

Key words: In Vitro Fertilization; Miscarriage; Ovarian Hyperstimulation Syndrome; Pregnancy Outcome; Pregnancy Rate

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproductive technology (ART) with development of multiple follicles. OHSS is characterized by cystic enlargement of the ovaries and an acute fluid shift from the intravascular compartment to the third space, which may result in ascites, pleural and/or pericardial infusion, and even generalized edema. OHSS patients suffer from lower abdominal discomfort, nausea, and vomiting. In severe cases of OHSS, thromboembolic events, acute respiratory distress syndrome (ARDS), and renal failure have been reported. Clinical practitioners are unsure whether OHSS and subsequent treatments, such as incessant pleural or abdominal punctures, volume expansion, and diuretics, would have an adverse effect on pregnancy outcomes of OHSS patients. Previous research on this topic had a lack of an appropriate contemporaneous control group, and there were potential confounders in the research, thus making interpretation of such data unclear. In the current study, based on consistent age and count of mature II (M-II) oocytes,
we compared pregnancy outcomes of patients with and without OHSS, and examined the possible effects of OHSS on pregnancy outcomes.

**Methods**

**Study subjects**

The *in vitro* fertilization (IVF) database was set up and maintained by research faculty members in our department. OHSS patients except for mild OHSS patients diagnosed and treated in our hospital from 2002 to 2012 were included, and basic information was recorded in the database. The research was approved by the College Institutional Review Board. Informed consent was not required because of the retrospective nature of this study.

The investigation was 1:1 and 1:2 retrospective cohort study. From 2002 to 2012, we identified 190 IVF patients with OHSS. In a total population of 5487 IVF fresh cycles, 197 contemporaneous non-OHSS cycles matched for age and count of M-II oocytes were selected as the unexposed group. The amount discrepancy of age and count of M-II oocytes between the two or three matching patients was no more than 2. The corresponding non-OHSS cycle occurred in the same or near month with the OHSS cycle.

**Inclusion and exclusion criteria**

OHSS can be classified into mild, moderate, severe, and critical ones. While in our study, we excluded the mild OHSS patients since they were treated outpatient. The severity of OHSS was defined according to the criteria proposed by Golan et al. and Navot et al. Moderate OHSS was characterized by abdominal distension and discomfort, nausea, vomiting or diarrhea, enlarged ovarian size (5–12 cm), and ultrasonic evidence of ascites. Severe OHSS was characterized by variable ovarian enlargement; massive ascites ± hydrothorax; hematocrit >45%; white blood cell count >15,000/ml; oliguria; creatinine 1.0–1.5 mg/dl; liver dysfunction; and anasarca. Critical OHSS was characterized by variable ovarian enlargement; tense ascites ± hydrothorax; hematocrit >55%; white blood cell count >25,000/ml; oliguria; creatinine ≥1.6 mg/dl; creatinine clearance <50 ml/min; renal failure; thromboembolic phenomena; and ARDS.

**Treatments**

OHSS patients were hospitalized. Intake and output volume, body weight, and abdominal circumference were recorded daily. Hematocrit, white blood cell count, and liver and kidney function indices were dynamically monitored. Changes in ovarian size and abdominal or pleural fluid were monitored by ultrasound when necessary. All of the patients were administered intravenous albumin or hydroxyethyl starch. Based on the status of disease, liver-protecting, anti-infection, and diuretic treatments, as well as drainage of abdominal and pleural fluid, were administered.

**Outcome indicators**

Pregnancy outcomes included clinical pregnancy, miscarriage, miscarriage of one twin, fetal intrauterine death, gestational age at birth, delivery mode, neonatal birth weight, and neonatal deformity. Clinical pregnancy met the standard of gestational sac under ultrasound diagnosis. Miscarriage included early- and late-term miscarriage. Early miscarriage occurred before 12 gestational weeks, and late-term miscarriage was between 13 and 28 gestational weeks. Premature delivery was defined as birth before 37 and after 28 completed weeks of pregnancy. Low birth weight (LBW) was defined as birth weight below 2500 g, and small-for-gestational age (SGA) was defined as a birth weight lower than the tenth percentile of the same gestational age of neonatal birth weight.

**Statistical analysis**

Data were expressed as mean ± standard deviation (SD), median (interquartile range), or n (%). Continuous variables were compared using Student’s *t*-test or Mann–Whitney *U*-test. Categorical variables were assessed using the Chi-square test. Logistic regression analysis was used to evaluate the association between OHSS and clinical pregnancy. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated after adjustment for controlled ovarian hyperstimulation (COH) protocol, gonadotropin (Gn) dosage, human chorionic gonadotropin (HCG) dose protocol on HCG day, luteal supporting protocol, polycystic ovary syndrome (PCOS), and anovulation. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., USA). A *P* < 0.05 was considered statistically significant.

**Results**

We identified 39 moderate (20.5%), 141 severe (74.2%), and 10 critical (5.3%) OHSS patients. The incidence of OHSS among 5487 fresh IVF cycles was 3.46%, and the rates of serious adverse events and thromboembolism in OHSS patients were 2.63% and 1.58%, respectively. The median duration of hospitalization was 11 days (2–73 days) and the mean number of abdominal and plural punctures was 3 (range: 0–18).

Comparison of IVF data between IVF patients with or without OHSS is shown in Table 1. The mean dosage of Gn used for ovulation induction for OHSS patients was lower than that of non-OHSS (*P* = 0.007). The clinical characteristics, including age, body mass index, diagnosis of infertility, and duration of infertility, were not significantly different between the two groups [Table 1]. Additionally, no significant difference was found in basal follicle-stimulating hormone or serum estradiol (E<sub>2</sub>) levels on HCG day between the groups.

Table 2 shows the outcomes of pregnancy. Seven patients with OHSS canceled embryo transfer (ET) because of early-onset severe OHSS, and 13 patients without OHSS canceled ET for a high risk of OHSS. Among the 183 OHSS patients who did undergo ET, 168 patients achieved clinical pregnancy with a clinical pregnancy rate of 91.8%, which was significantly higher than that in the control group (43.5%, *P* < 0.001). The rates of multiple pregnancy and miscarriage...
were not significantly different between the two groups, and all the triplets and quadruplets were surgically reduced to twins during 9–12 weeks of gestational age.

The delivery outcomes of 138 OHSS live births (84 singletons, 54 twins) were compared with those of the control group, which were 63 live births (41 singletons, 22 twins). We found no significant differences in the rates of live birth (82.1% vs. 78.8%), preterm delivery (20.9% vs. 17.5%), preterm birth before 34 weeks’ gestation (8.6% vs. 7.9%), singleton LBW (9.5% vs. 4.9%), and singleton SGA (7.1% vs. 7.3%) between the two groups. The pregnancy outcomes of five critical OHSS patients are shown in Table 3.

Table 1: Comparison of IVF data between OHSS and non-OHSS groups

| Items                                | OHSS group (n = 190) | Non-OHSS group (n = 197) | P    |
|--------------------------------------|----------------------|--------------------------|------|
| Age (years)                          | 32.0 ± 4.0           | 32.0 ± 3.8               | 0.871|
| BMI (kg/m²)                          | 21.9 ± 3.0           | 22.1 ± 2.8               | 0.533|
| Nulligravida, n (%)                  | 107 (56.3)           | 112 (56.9)               | 0.915|
| Duration of infertility (years), median (IQR) | 4 (2–6)          | 4 (2–6)                  | 0.868|
| Indication for IVF, n (%)            | 50 (26.3)            | 42 (21.3)                | 0.248|
| PCOS                                 | 21 (11.1)            | 27 (13.7)                | 0.428|
| Tubal                                | 78 (41.1)            | 84 (42.6)                | 0.752|
| Male                                 | 84 (44.2)            | 86 (43.7)                | 0.912|
| Endometriosis                        | 34 (17.9)            | 33 (16.8)                | 0.766|
| Unexplained                          | 3 (1.6)              | 3 (1.5)                  | 1.000|
| Multiple                              | 62 (32.6)            | 54 (27.4)                | 0.262|
| Basal FSH (μU/ml)                    | 6.49 ± 1.89          | 6.81 ± 2.18              | 0.125|
| COH protocol, n (%)                  |                      | 0.206                    |      |
| Long protocol                        | 109 (57.4)           | 103 (52.3)               |      |
| Short protocol                       | 21 (11.1)            | 37 (18.8)                |      |
| Ultra-long protocol                  | 22 (11.6)            | 20 (10.2)                |      |
| Step-down long protocol              | 38 (20.0)            | 37 (18.8)                |      |
| Gn dosage (U)                        |                      | 2255 ± 773               | 0.007*|
| Serum E₂ on HCG day (pg/ml)          | 3823 ± 2358          | 3513 ± 1560              | 0.162|
| HCG dose on HCG day, n (%)           | 0.272                |                         |      |
| HCG 10,000 IU                        | 118 (62.1)           | 134 (68.0)               |      |
| HCG 5000 IU                          | 14 (7.4)             | 8 (4.1)                  |      |
| rHCG                                 | 58 (30.5)            | 55 (27.9)                |      |
| Count of M-II oocytes, median (IQR)  | 13 (10–16)           | 13 (10–16)               | 0.743|
| Embryos retrieved, median (IQR)      | 12 (9–15)            | 12 (9–15)                | 0.891|
| Embryos transferred, median (IQR)    | 2 (2–3)              | 2 (2–3)                  | 0.089|
| Luteal supporting protocol, n (%)    |                      | 0.111                    |      |
| Progesterone                         | 10 (5.5)             | 3 (1.6)                  |      |
| Progesterone with HCG                | 166 (90.7)           | 176 (95.7)               |      |
| Progesterone with rHCG               | 7 (3.8)              | 5 (2.7)                  |      |
| HCG dose for luteal-sup (U)          | 2343 ± 1740          | 3443 ± 2201              | <0.001|

Data were showed as mean ± SD, median (IQR), or n (%). OHSS: Ovarian hyperstimulation syndrome; BMI: Body mass index; IVF: In vitro fertilization; PCOS: Polycystic ovary syndrome; FSH: Follicle-stimulating hormone; COH: Controlled ovarian hyperstimulation; Gn: Gonadotropin; HCG: Human chorionic gonadotropin; rHCG: Recombinant human chorionic gonadotropin; M-II: Mature-II; IQR: Interquartile range; E₂: Estradiol; SD: Standard deviation.

Table 2: Comparison of pregnancy outcomes between OHSS and non-OHSS group

| Items                                | OHSS group (n = 190) | Non-OHSS group (n = 197) | P    |
|--------------------------------------|----------------------|--------------------------|------|
| Transferring cycles                  | 183 (96.3)           | 184 (93.4)               | 0.195|
| Clinical pregnancy                   | 168 (91.8)           | 80 (43.5)                | <0.001|
| Singletons                           | 89 (53.0)            | 46 (57.5)                | 0.800|
| Twins                                | 72 (43.0)            | 31 (38.8)                |      |
| Triplets                             | 7 (4.0)              | 2 (2.5)                  | 1.000|
| Quadruplets                          | 0 (0)                | 1 (1.2)                  |      |
| Miscarriage                          | 25 (14.9)            | 13 (16.3)                | 0.777|
| Miscarriage of one twin              | 17 (10.1)            | 8 (10.0)                 | 0.977|
| Intrauterine fetal death             | 2 (1.2)              | 1 (1.3)                  | 1.000|
| Live-birth                           | 138 (82.1)           | 63 (78.8)                | 0.524|
| Singletons                           | 84 (60.9)            | 41 (65.1)                | 0.568|
| Twins                                | 54 (39.1)            | 22 (34.9)                |      |
| Preterm delivery                     | 29 (20.9)            | 11 (17.5)                | 0.574|
| Birth before 34 weeks                | 12 (8.6)             | 5 (7.9)                  | 0.869|
| Delivery week                        | 37.7 ± 2.3           | 37.7 ± 2.0               | 0.951|
| Mode of delivery                     |                      |                         |      |
| Cesarean section                     | 118 (84.9)           | 53 (84.1)                | 0.889|
| Vaginal delivery                     | 21 (15.1)            | 10 (15.9)                |      |
| Neonatal births                      | 192                  | 85                       |      |
| Neonatal deaths                      | 2 (1.0)              | 0 (0)                    | 1.000|
| Birth weight (g)                     | 2813 ± 620           | 2880 ± 607               | 0.401|
| LBW                                  | 58 (30.2)            | 20 (23.5)                | 0.254|
| SGA                                  | 42 (21.9)            | 15 (17.6)                | 0.422|
| Singleton LBW                        | 8 (9.5)              | 2 (4.9)                  | 0.584|
| Singleton SGA                        | 6 (7.1)              | 3 (7.3)                  | 1.000|
| Neonatal deformity                   | 0 (0)                | 1 (1.2)                  | 0.307|

Data were showed as mean ± SD or n (%). LBW: Low birth weight; SGA: Small-for-gestational age; OHSS: Ovarian hyperstimulation syndrome; CI: Confidence interval.

Thereafter, we compared IVF data of moderate OHSS, severe/critical OHSS with that of non-OHSS patients, respectively [Table 4]. The proportion of different COH protocol was statistically different between severe/critical OHSS and non-OHSS patients (P = 0.039). The proportion of short protocol was comparatively higher in non-OHSS than severe/critical OHSS patients. After controlling for COH protocol, Gn dosage, HCG dose on HCG day, luteal supporting protocol, PCOS, and anovulation, OHSS was associated with increased probability of clinical pregnancy. The adjusted ORs of moderate OHSS and severe/critical OHSS for clinical pregnancy were 4.65 (95% CI, 1.86–11.61) and 5.83 (95% CI, 3.45–9.86), respectively.

Discussion

ART has been carried out for more than 30 years. Clinical practitioners have always been committed to improving ovarian stimulation protocols to keep the incidence of OHSS no more than 5%. However, critical OHSS occasionally occurs, including acute renal failure, thrombosis, stroke, pulmonary edema, myocardial...
infarction, ARDS, and even maternal death. Considering OHSS-associated complications, clinical practitioners and patients need to determine whether to terminate pregnancy because this would substantially alleviate the condition of OHSS patients. While most patients choose to continue pregnancy because this disease is self-limited, they are also wondering whether OHSS would bring adverse impact to pregnancy.

A previous study has demonstrated that OHSS is more likely to occur at a younger age and in treatment cycles with the highest ovarian response to stimulation. Additionally, infertility is an independent factor that appears to be involved with a poor obstetric outcome. Furthermore, age is the primary determinant of live births. The oocyte yield, independent of age, shows a linear relationship with live births with up to 15 oocytes in IVF cycles. Therefore, to exclude potential bias, we matched age and count of M-II oocytes.

### Table 3: Pregnancy and maternal outcome of OHSS patients with major complications

| Patients number | Adverse events | Pregnancy outcomes | Maternal outcomes |
|-----------------|----------------|--------------------|-------------------|
| 1               | Brachial arterial thrombosis | Live birth | Alleviated after therapy |
| 2               | Calf muscular venous thrombosis | Live birth | Alleviated after therapy |
| 3               | Cerebral infarction | Termination | Mixed aphasia |
| 4               | ARDS | Live birth | Alleviated after therapy |
| 5               | Type-I respiratory failure | Failure | Alleviated after therapy |

ARDS: Acute respiratory distress syndrome; OHSS: Ovarian hyperstimulation syndrome.

### Table 4: Comparison of IVF data among moderate, severe/critical OHSS and non-OHSS patients

| Items | Non-OHSS group (n = 197) | Moderate OHSS (n = 39) | Severe/critical OHSS (n = 151) | P₁ | P₂ |
|-------|--------------------------|------------------------|-------------------------------|----|----|
| Age (years) | 32.0 ± 3.8 | 32.0 ± 4.4 | 32.0 ± 4.0 | 0.929 | 0.875 |
| BMI (kg/m²) | 22.1 ± 2.8 | 22.0 ± 3.3 | 21.9 ± 2.9 | 0.643 | 0.490 |
| Nulligravida, n (%) | 112 (56.9) | 21 (53.8) | 86 (57.0) | 0.729 | 0.985 |
| Duration of infertility (years), median (IQR) | 4 (2–6) | 5 (3–8) | 4 (2–6) | 0.027 | 0.757 |
| Indication for IVF, n (%) | | | | | |
| Anovulation | 42 (21.3) | 8 (20.5) | 42 (27.8) | 0.910 | 0.161 |
| PCOS | 27 (13.7) | 8 (20.5) | 13 (8.6) | 0.274 | 0.140 |
| Tubal | 84 (42.6) | 14 (35.9) | 64 (42.4) | 0.435 | 0.962 |
| Male | 86 (43.7) | 22 (56.4) | 62 (41.1) | 0.144 | 0.627 |
| Endometriosis | 33 (16.8) | 5 (12.8) | 29 (19.2) | 0.542 | 0.553 |
| Unexplained | 3 (1.5) | 1 (2.6) | 2 (1.3) | 0.517 | 1.000 |
| Multiple | 54 (27.4) | 13 (33.3) | 49 (32.5) | 0.454 | 0.307 |
| Basal FSH (μU/ml) | 6.81 ± 2.18 | 6.32 ± 1.33 | 6.53 ± 2.01 | 0.171 | 0.256 |
| COH protocol, n (%) | | | | 0.866 | 0.039 |
| Long protocol | 103 (52.3) | 21 (53.8) | 88 (58.3) | | |
| Short protocol | 37 (18.8) | 9 (23.1) | 12 (7.9) | | |
| Ultra-long protocol | 20 (10.2) | 3 (7.7) | 19 (12.6) | | |
| Step-down long protocol | 37 (18.8) | 6 (15.4) | 32 (21.2) | | |
| Gn dosage (U) | 2477 ± 830 | 2262 ± 834 | 2254 ± 760 | 0.120 | 0.007 |
| Serum E₂ on HCG day (pg/ml) | 3513 ± 1560 | 4414 ± 3998 | 3670 ± 1686 | 0.084 | 0.356 |
| Basal FSH (μU/ml) | 6.81 ± 2.18 | 6.32 ± 1.33 | 6.53 ± 2.01 | 0.171 | 0.256 |
| Luteal supporting protocol, n (%) | | | | 0.866 | 0.039 |
| Progesterone | 134 (68.0) | 19 (48.7) | 99 (65.6) | | |
| rHCG | 55 (27.9) | 14 (35.9) | 44 (29.1) | | |
| Count of M-II oocytes, median (IQR) | 13 (10–16) | 13 (10–17) | 13 (10–16) | 0.469 | 0.956 |
| Embryos retrieved, median (IQR) | 12 (9–15) | 11 (10–17) | 12 (9–15) | 0.703 | 0.804 |
| Embryos transferred, median (IQR) | 2 (2–3) | 2 (2–3) | 2 (2–3) | 0.642 | 0.065 |
| HCG dose for luteal-sup (U) | 3443 ± 2201 | 2517 ± 1271 | 2306 ± 1825 | 0.071 | <0.001 |

Data were showed as mean ± SD, median (IQR), or n (%). P represents moderate OHSS compared with non-OHSS patients and Pᵋ represents severe/critical OHSS compared with non-OHSS patients. OHSS: Ovarian hyperstimulation syndrome; BMI: Body mass index; IVF: In vitro fertilization; PCOS: Polycystic ovary syndrome; FSH: Follicle-stimulating hormone; COH: Controlled ovarian hyperstimulation; Gn: Gonadotropin; HCG: Human chorionic gonadotropin; rHCG: Recombinant human chorionic gonadotropin; M-II: Mature-II; IQR: Interquartile range; E₂: Estradiol; SD: Standard deviation.
stimulation and HCG for luteal support was significantly lower in OHSS patients than in non-OHSS patients, which suggested that OHSS patients were more sensitive to stimulatory drugs.

Multiple studies have reported that the clinical pregnancy rate in OHSS patients is significantly higher than that in general IVF patients or non-OHSS patients.\[^{13-17}\] This finding is similar to our results. To a great extent, pregnancy triggers and aggravates OHSS, and this is called late-term onset OHSS. Late OHSS is triggered by endogenous HCG release in the event of pregnancy, generally occurring after 9–10 days following HCG injection. Early OHSS is caused by administration of exogenous HCG, which appears to be associated with an excessive ovarian response to Gn stimulation, generally occurring before the 9\(^{th}\) and 10\(^{th}\) day after HCG injection.\[^{15}\] Because we performed a retrospective study, it is difficult to define the onset model according to patients’ subjective recall.

In terms of pregnancy outcome, the rates of miscarriage and perinatal complications including preterm birth, SGA, pregnancy-induced hypertension and/or stillbirth were significantly higher in OHSS group than non-OHSS group, as reported in literature. We analyzed that it was probably the relatively higher rate of multiple pregnancy that induced massive perinatal complications [Table 5]. Pregnancy and multiple pregnancies dramatically worsen the situation of OHSS patients.\[^{13}\] Similar miscarriage rates between groups were observed after excluding this confounder in our study and Courbiere’s series.\[^{19}\]

Some authors have postulated that systemic vascular dysfunction and microthromboembolic events might affect trophoblastic invasion, leading to placental insufficiency.\[^{19}\] Thromboembolic events occurred in four of the 40 OHSS pregnant patients in Courbiere’s study, characterized by increased thromboembolic events up to 10\(^{th}\), with a comparably higher rate of preterm than non-OHSS pregnant patients.\[^{19}\] We may hypothesize that this seemingly higher rate of preterm may be due to thrombosis. Not all of the thrombosis in IVF patients was correlated with OHSS, and IVF pregnant patients complicated by OHSS had an increased risk of arterial thrombosis.\[^{11}\] Therefore, OHSS and pregnancy could be viewed as precipitating factors for thrombosis in IVF.\[^{20}\]

Supraphysiological ovarian stimulation results in E\(_2\) levels greater than those in natural conception (NC) cycles and causes E\(_2\) levels in the early stage to be similar to those in the late stage of the first trimester of NC.\[^{12}\] Previous studies showed that the high maternal E\(_2\) environment in the first trimester was correlated with increased risks of LBW and SGA.\[^{21}\] Additionally, the birth rates of singleton LBW and singleton SGA of fresh ET were significantly higher than those of frozen ET and NC (6.3\%, 4.4\%, and 3.6\%, and 6.9\%, 5.0\%, and 4.8\%, respectively).\[^{21}\] Large-scale studies in China on the epidemiology of SGA and LBW are still lacking. Some hospital-based studies and regional investigations have described that the rate of preterm birth ranges from 3.1\% to 5.8\%, LBW is 1.6\%, and SGA is 2.9\%.\[^{22,23}\] In the aggregate series, the rate of singleton preterm birth was 8.8\%, singleton LBW was 8.0\%, and singleton SGA was 7.2\%. Generally, rates of preterm birth and LBW or SGA were higher in IVF cycles than in NC.

In conclusion, OHSS, which occurs in the luteal phase or early pregnancy of IVF patients and represents transient abnormal hemodynamics, was not found to exert any obviously adverse effect on the subsequent pregnancy. However, whether OHSS would exert adverse effect on the offsprings of IVF mothers in the long-term, required further studies.

**Acknowledgments**

We appreciate the reproductive endocrinologists and gynecologists at Peking Union Medical College Hospital for their diligent clinical work and precise data recording about the cases we reported in this article.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

---

**Table 5: Comparison of pregnancy outcome between OHSS and non-OHSS group, literature review**

| Studies                          | Thrombosis rate | Multiple pregnancy rate | Clinical pregnancy rate | Miscarriage rate | Perinatal complication |
|----------------------------------|-----------------|-------------------------|-------------------------|------------------|------------------------|
| Abramov et al. (1998)            | 2.5\%           | 24% versus 3–5%         | 73.2% versus 14.4%      | 29.5% versus 18.0–22.0% | Preterm (44% vs. 24–29%); LBW (62.1% vs. 24–36%); PIH (13.2% vs. 6.0%) |
| Mathur and Jenkins (2000)        | –               | 36.1% versus 27.4%      | –                       | 12.1% versus 16.8% | –                      |
| Luke et al. (2010)               | –               | 58–86%\(^{\dagger}\)   | 98–168%\(^{\dagger}\)   | –                | Preterm birth; LBW Stillbirth; 26–31%\(^{\dagger}\) |
| Courbiere et al. (2011)          | 10%             | 2.5% versus 2.5%        | –                       | 17.5% versus 16%  | Preterm (36.0% vs. 10.7%); PIH (21.2% vs. 9.2%) |
| Current study                    | 1.58%           | 4.0% versus 3.7%        | 91.8% versus 45.1%      | 14.9% versus 16.3% | No difference          |

\(^{\dagger}\) Data not mentioned. \(\dagger\) Compared with non-OHSS patients, the multiple pregnancy rate of OHSS patients increased 58%–86%; the rate of perinatal complication including preterm birth, LBW and stillbirth, of OHSS patients increased 26–31%. \(^{\dagger}\) Compared with non-OHSS patients, the clinical pregnancy rate of OHSS patients increased 98%–168%. PIH: Pregnancy-induced hypertension; LBW: Low birth weight; OHSS: Ovarian hyperstimulation syndrome.
REFERENCES

1. Vloeberghs V, Peeraer K, Pexsters A, D’Hooghe T. Ovarian hyperstimulation syndrome and complications of ART. Best Pract Res Clin Obstet Gynaecol 2009;23:691-709.
2. Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: An update review. Obstet Gynecol Surv 1989;44:430-40.
3. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: Prevention and treatment. Fertil Steril 1992;58:249-61.
4. Marak CP, Chopra A, Alappan N, Ponea AM, Guddati AK. Ovarian hyperstimulation syndrome as an etiology of obstructive uropathy. Case Rep Obstet Gynecol 2013;2013:653704.
5. Jing Z, Yanping L. Middle cerebral artery thrombosis after IVF and ovarian hyperstimulation: A case report. Fertil Steril 2011;95:2435.e13-5.
6. Fleming T, Sacks G, Nasser J. Internal jugular vein thrombosis following ovarian hyperstimulation syndrome. Aust N Z J Obstet Gynaecol 2012;52:87-90.
7. Bartkova A, Sanak D, Dostal J, Herzig R, Otruba P, Vlachova I, et al. Acute ischaemic stroke in pregnancy: A severe complication of ovarian hyperstimulation syndrome. Neurol Sci 2008;29:463-6.
8. Semba S, Moriya T, Youssef EM, Sasano H. An autopsy case of ovarian hyperstimulation syndrome with massive pulmonary edema and pleural effusion. Pathol Int 2000;50:549-52.
9. Akdemir R, Uyan C, Eminioglu Y. Acute myocardial infarction secondary thrombosis associated with ovarian hyperstimulation syndrome. Aust N Z J Obstet Gynaecol 2012;52:83:187-9.
10. Fineschi V, Neri M, Di Donato S, Pomara AM, Rizzuto A, et al. An immunohistochemical study in a fataality due to ovarian hyperstimulation syndrome. Int J Leg Med 2010:124:293-9.
11. Braat DD, Schutte JM, Bernardus RE, Moolij TM, van Leeuwen FE. Maternal death related to IVF in the Netherlands 1984-2008. Hum Reprod 2010;25:1782-6.
12. Mathur RS, Jenkins JM. Is ovarian hyperstimulation syndrome associated with a poor obstetric outcome? J Pregnancy 2000;107:943-6.
13. McDonald SD, Murphy K, Beyene J, Olsson A. Perinatal outcomes of singleton pregnancies achieved by in vitro fertilization: A systematic review and meta-analysis. J Obstet Gynaecol Can 2005;27:449-59.
14. Aboulghar M, Saber W, Amin Y, Aboulghar MM, Serour G, Mansour R. Impact of anti Müllerian hormone assays on the outcomes of in vitro fertilization: A prospective controlled study. Fertil Steril 2014;101:134-7.
15. Abramov Y, Elchalal U, Schenker JG. Obstetric outcome of in vitro fertilized pregnancies complicated by severe ovarian hyperstimulation syndrome: A multicenter study. Fertil Steril 1998;70:1070-6.
16. Raziel A, Friedler S, Schachter M, Strassburger D, Mordechai E, Ron-El R. Increased early pregnancy loss in IVF patients with severe ovarian hyperstimulation syndrome. Hum Reprod 2002;17:107-10.
17. Luke B, Brown MB, Morbeck DE, Hudson SB, Coddington CC 3rd, Stern JE. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on assisted reproductive technology (ART) treatment and outcome. Fertil Steril 2010;94:1399-404.
18. Lee KH, Kim SH, Jee BE, Kim YJ, Suh CS, Kim KC, et al. Comparison of clinical characteristics between early and late patterns in hospitalized patients with ovarian hyperstimulation syndrome. Fertil Steril 2010;93:2274-80.
19. Courbiere B, Oborski V, Braunstein D, Desparoir A, Noizet A, Garnerre M. Obstetric outcome of women with in vitro fertilization pregnancies hospitalized for ovarian hyperstimulation syndrome: A case-control study. Fertil Steril 2011;95:1629-32.
20. Hansen AT, Kesmodel US, Juul S, Hvas AM. Increased venous thrombosis incidence in pregnancies after in vitro fertilization. Hum Reprod 2014;29:611-7.
21. Hu XL, Feng C, Lin XH, Zhong ZX, Zhu YM, Lv PP, et al. High maternal serum estradiol environment in the first trimester is associated with the increased risk of small-for-gestational-age birth. J Clin Endocrinol Metab 2014;99:2217-24.
22. Newnham JP, Sahota DS, Zhang CY, Xu B, Zheng M, Doherty DA, et al. Preterm birth rates in Chinese women in China, Hong Kong and Australia—the price of Westernisation. Aust N Z J Obstet Gynaecol 2011;51:426-31.
23. Sun L, Tao F, Hao J, Su P, Liu F, Xu R. First trimester vaginal bleeding and adverse pregnancy outcomes among Chinese women: From a large cohort study in China. J Matern Fetal Neonatal Med 2012;25:1297-301.