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Research Paper

## Reduced Intellectual Ability in Offspring of Ovarian Hyperstimulation Syndrome: A Cohort Study

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### ABSTRACT

**Background:** Ovarian hyperstimulation syndrome (OHSS), a complication of ovarian stimulation, has various adverse effects on both pregnant women and their offspring. However, whether OHSS will affect intellectual ability in offspring is still unknown.

**Methods:** We recruited 86 Chinese children born to OHSS women and 172 children conceived with non-OHSS In Vitro Fertilization (IVF) in this cohort study. Their intellectual ability was assessed according to the Revised Chinese Version of the Wechsler Intelligence Scale for Children (C-WISC). Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ), and Full Intelligence Quotient (FIQ) were calculated. The investigation was registered in Chinese Clinical Trial Registry (ChiCTR-SOC-16009555).

**Findings:** OHSS offspring scored less on C-WISC (mean (standard deviation [SD]): (VIQ = 92.7 (14.7), PIQ = 108.9 (13.1), FIQ = 100.6 (13.4)) compared with non-OHSS IVF offspring (VIQ = 100.1 (13.2), PIQ = 113.7 (10.8), FIQ = 107.4 (11.5)). The prevalence of low IQ (<80) children was 4.7 times higher in OHSS offspring compared with non-OHSS offspring. Maternal estradiol level on hCG administration day was negatively associated with FIQ in offspring.

**Interpretation:** OHSS offspring displayed reduced intellectual ability. Prenatal estradiol exposure might be involved in underlying mechanism.

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### 1. Introduction

The long-term safety of assisted reproductive technologies (ARTs) - related offspring always draws attention. Most of previous studies reported generally normal intellectual ability in ARTs toddlers, preschoolers, and children in middle childhood (Bay et al., 2013). In contrast, some studies found that ARTs children scored lower in intellectual tests (Knoester et al., 2008; Zhu et al., 2009; Sutcliffe et al., 2001).

Ovarian over-response to ovarian stimulation during ARTs leads to ovarian hyperstimulation syndrome (OHSS). The prevalence of moderate or severe OHSS varies from 0.5% to 6% in different studies (Delvigne and Rozenberg, 2002). OHSS is characterized by elevated estradiol level,

cystic ovarian enlargement, and fluid shift from the intravascular compartment into the peritoneal, pleural or pericardial cavities during the first trimester (Nastri et al., 2010). Since ovarian stimulation and ARTs have been widely performed (1% to 4% of births in developed countries) (Sutcliffe and Ludwig, 2007), more children are born under the potential jeopardy of ovarian hyperstimulation.

Offspring of OHSS or ARTs displayed abnormality in several aspects. ARTs are associated with higher risks of low birth weight and small-for-gestational-age birth (Hu et al., 2014). Offspring after exposure to high estradiol environment in ARTs displayed altered thyroid hormone profile (Lv et al., 2014). The OHSS offspring displayed cardiovascular dysfunction (Xu et al., 2014). A recent study published on JAMA showed that cardiovascular risk factors were associated with dementia in adults (Gottesman, 2017 #1757). Although the population in our study were much younger, we were curious to know whether intellectual outcomes of OHSS children were affected. Therefore, we performed intellectual evaluation on OHSS children to study the potential harm of OHSS in early intellectual development.

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## 2. Materials and Methods

### 2.1. Study Design and Participants

Reproductive information of patients who underwent in-vitro fertilization (IVF) at reproductive center, women's hospital, Zhejiang University was extract from inpatient database. Eligible women were those underwent IVF and suffered from severe OHSS between Jan 2005 and Dec 2007. Exclusion criteria were: data missed in database, age over 40 or age of husband over 40 at the time of IVF, either of the couple smoked or abused alcohol (>14 drinks/weeks for women and >21 drinks/week for men) within 3 months before IVF, abortion, fetal loss, stillbirth, neonatal death or fetal major congenital malformations. After exclusion, 106 OHSS women were invited to participate in the study. A total of 86 women agreed to participate and 99 children completed the IQ tests. We created a 1:2 matched control cohort comprising IVF women without OHSS (non-OHSS IVF) and their children. The matching factors were multiple birth, gestational age (within one week), birth weight (within 100 g) and age of children (within 6 months). If a woman in control group refused to participate, we invited another matched woman to ensure the 1:2 ratio. To prevent the correlation between twins, we included only one twin from each pair of twins. An online randomization tool ([www.randomizer.org](http://www.randomizer.org)) was used to select the twin from OHSS group ([www.randomizer.org](http://www.randomizer.org)), and

matched them with children from non-OHSS IVF group. Eighty six children of OHSS group and 172 children of non-OHSS group were included in final analysis. (Fig. 1).

OHSS was diagnosed and classified according to Golan and Wasserman's 2009 criteria (Golan and Weissman, 2009). Briefly, if one of the following 3 criteria is met, the women can be diagnosed as severe OHSS: 1) clinical evidence of ascites or hydrothorax or breathing difficulties, 2) depletion in blood volume and haemoconcentration, 3) severe complications such as renal failure, thromboembolism and acute respiratory distress syndrome. All OHSS cases were fresh embryo transfer IVF.

The women were contacted by telephone. Parental, delivery and ARTs characteristics were collected through parental interview and review of medical records. Height and weight of children were measured during the interview. Parental education level was classified as: low (middle school or below), middle (high school), and high (college or above). Primary infertility is defined as the inability to ever become pregnant after at least one year of having sex and not using birth control methods. Secondary infertility is defined as the inability to become pregnant after at least one year having sex without using birth control methods, following the birth of one or more biological children.

The Ethics Committee of Women Hospital, School of Medicine, Zhejiang University approved the study. Written informed consents were obtained from the parents of these children. The investigation was registered in Chinese Clinical Trial Registry (ChiCTR-SOC-16009555).

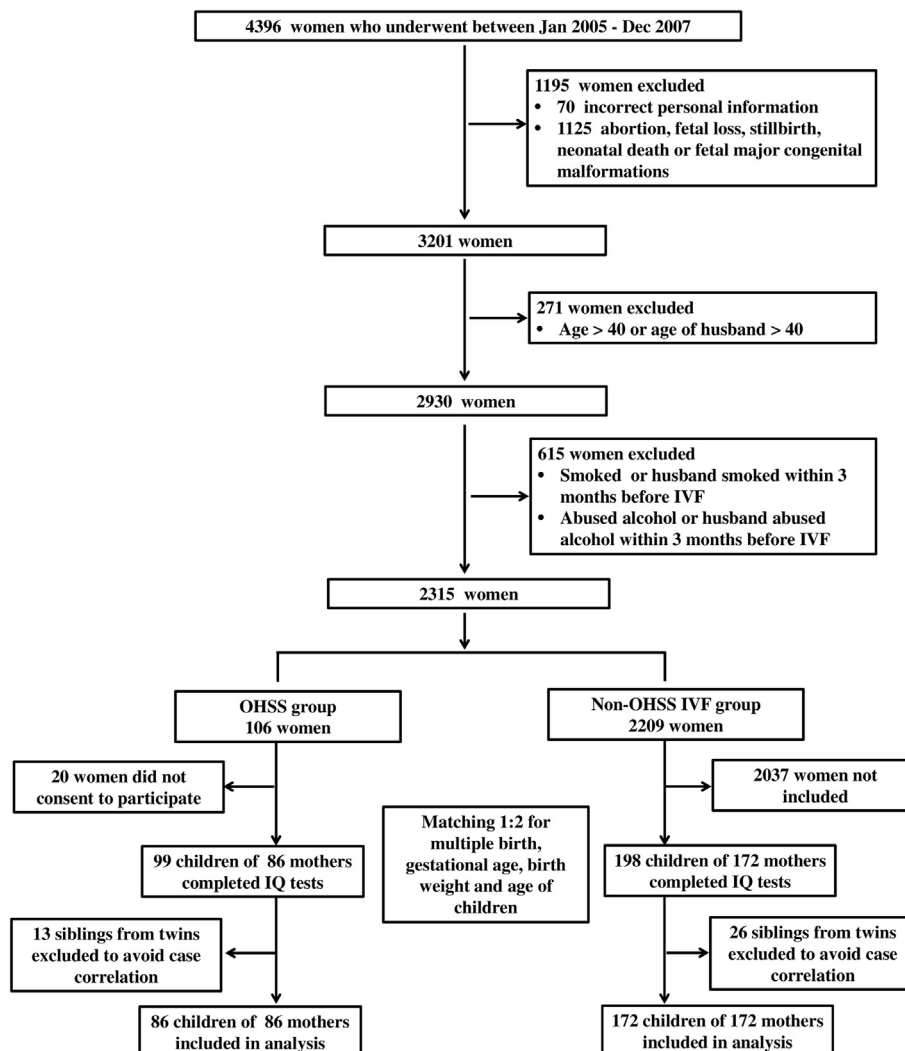


Fig. 1. Study design.

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