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.

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, pre-schoolers, 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) was used to select the twin from OHSS group (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).
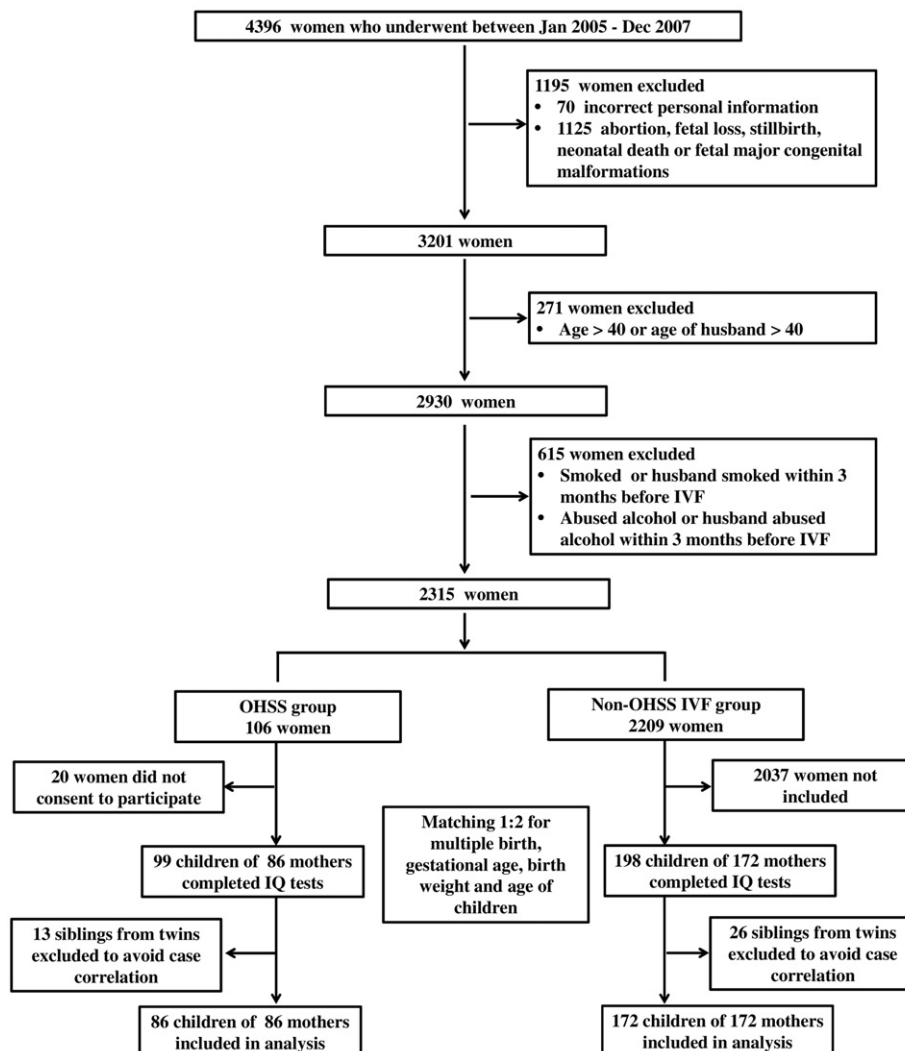

Fig. 1. Study design.

2.2. Evaluation of Intellectual Ability

The intellectual ability was assessed according to the Chinese Version of the Wechsler Intelligence Scale for Children-Revised (C-WISC) (Yu et al., 2012). All children completed 10 individual subtests, including 5 verbal tests and 5 performance tests. The verbal tests includes Arithmetic (A), Comprehension (C), Information (I), Sorting (S) and Vocabulary (V), and the performance tests includes Animal Pegs (AP), Block Design (BD), Mazes (MA), Object Assembly (OA) and Picture Completion (PC). After the intelligence subtests, the raw score from each subtest was transformed into a scaled score and the following 3 intelligence quotients (IQs) were calculated: Verbal Intelligence Quotient (VIQ, transformed from the sum of scaled verbal scores), Performance Intelligence Quotient (PIQ, transformed from the sum of scaled performance scores), and Full Intelligence Quotient (FIQ, transformed from the total sum of scaled scores). The score was standardized based on a sample of 3320 Chinese children, comprising multiple age groups, districts and parental education levels. All intelligence tests were administered by trained professionals who were blinded to the study grouping.

2.3. Statistical Analysis

Data obtained from intelligence tests were analyzed using SPSS 18.0 (IBM, USA). We compared continuous variables using Student's t-test or ANOVA with Turkey post-hoc analysis. Categorical variables were compared by using two-tailed Chi-square tests, or Fisher's exact test. FIQ, VIQ and PIQ were expressed as mean (standard deviation [SD]). The mean differences were adjusted to control for certain confounders according to different models with linear regression model. Model 1 adjusted for child age, gestational age, birth weight, maternal age, nulliparous, maternal PCOS, maternal education, paternal age, paternal education, gestational diabetes, preeclampsia, intrahepatic cholestasis of pregnancy, apgar score < 7, and respiratory distress syndrome. Model 2 additional adjusted for maternal estradiol level on hCG administration day. All reported P values are two-sided. Power calculation was performed before the study on the basis of our previously reported IQs of IVF children (Xing et al., 2014). Considering score difference of 5 in FIQ between OHSS and non-OHSS IVF subjects (SD = 10; power > 0.9; α = 0.05; sampling ratio = 2), 63 OHSS cases and 126 non-OHSS IVF cases were required.

3. Results

3.1. Baseline Characteristics

Characteristics of the study population are shown in Table 1 and Table 2. The age, gender, height, weight, BMI, gestational complications, and delivery data were similar between non-OHSS IVF and OHSS groups (Table 1). Maternal and paternal data were similar between two groups except for serum estradiol level on hCG administration day (Table 2).

3.2. Lower Intelligence Quotients in OHSS Offspring

Intellectual ability was evaluated with C-WISC (Table 3). Offspring from OHSS group scored lower in both VIQ and PIQ. FIQ of OHSS offspring was 6.8 (95%CI 3.6–9.9) lower than that of non-OHSS IVF offspring (Unadjusted). We used multivariable analysis with a linear regression model to control for potential confounding factors and assess effect of prognostic factor. In model 1, we adjusted for child age, gestational age, birth weight, maternal age, nulliparous, maternal PCOS, maternal education, paternal age, paternal education, gestational diabetes, preeclampsia, intrahepatic cholestasis of pregnancy, apgar score < 7 and respiratory distress syndrome. FIQ of OHSS offspring was 6.6 (95%CI 3.3–9.9) lower than that of non-OHSS IVF offspring after model 1 adjustment. In model 2, we additionally adjusted for maternal estradiol level on hCG administration day. Difference were insignificant after model 2 adjustment.

Table 1
Baseline characteristics of children and prenatal outcomes.

Characteristic	Non-OHSS IVF (N = 172)	OHSS (N = 86)	P value
Age, yr	4.97 (0.14)	4.95 (0.53)	NA
Male, N (%)	90 (52.3)	41 (47.7)	0.481
Height, cm	111.6 (4.3)	110.6 (5.0)	0.116
Weight, kg	19.0 (2.5)	18.6 (2.7)	0.238
BMI, kg/m^2	15.2 (1.5)	15.1 (1.3)	0.708
Gestational complications			
Gestational diabetes	30 (19.8)	13 (15.1)	0.636
Preeclampsia	9 (5.2)	7 (8.1)	0.361
Intrahepatic cholestasis of pregnancy	13 (7.6)	7 (8.1)	0.869
Delivery data			
Gestational age at delivery, wk	37.8 (2.0)	37.8 (1.6)	NA
Birth weight, g	3135 (610)	3068 (521)	NA
Cesarean section, N (%)	92 (53.5)	42 (48.9)	0.566
Apgar score < 7 at 5 min, N (%)	4 (2.3)	2 (2.3)	1.000
Respiratory distress syndrome, N (%)	1 (0.5)	1 (1.0)	0.801

IVF, In Vitro Fertilization; OHSS, ovarian hyperstimulation syndrome; BMI, body mass index; PCOS, polycystic ovarian syndrome. NA, not applicable. Data are mean (standard deviation) or number (percent). Matching factors (age, gestational age and birth weight) were not tested. For gestational complications, case number are 172 (IVF) and 86 (OHSS). P values were calculated by independent Student t-test, Chi-square test or Fisher's exact test.

3.3. Increased Risk of Intellectual Disability in OHSS Offspring

We investigated the prevalence of intellectual disability (IQ < 80) between groups. As shown in Table 4, OHSS offspring showed elevated prevalence of intellectual disability in verbal (19.8% vs 7.0%), performance (4.7% vs 0%) and full IQ (8.1% vs 1.7%) compared with non-OHSS IVF offspring.

3.4. Higher Estradiol is Associated With Lower Intelligence Quotients in OHSS Offspring

To further investigate the effect of prenatal estradiol exposure on offspring IQ, both non-OHSS IVF group and OHSS group were divided into low estradiol and high estradiol subgroups by the 75th percentile

Table 2
Parental characteristics.

Characteristic	Non-OHSS IVF (N = 172)	OHSS (N = 86)	P value
Maternal factors			
Maternal Age, yr	29.6 (3.3)	29.8 (3.8)	0.568
Nulliparous, N (%)	135 (78.5)	68 (79.1)	0.914
Maternal BMI at delivery, kg/m2	27.8 (3.1)	27.3 (3.6)	0.328
Maternal estradiol level on hCG administration day, pmol/L	12,213 (3417)	16,159 (4789)	<0.001
PCOS, N (%)	34 (19.8)	23 (26.7)	0.203
Maternal education level			
Low, N (%)	23 (13.4)	16 (18.6)	0.396
Middle, N (%)	68 (39.5)	36 (41.9)	
High, N (%)	81 (47.1)	34 (39.5)	
Type of infertility			0.582
Primary infertility	112 (65.1)	53 (61.6)	
Secondary infertility	60 (34.9)	33 (38.4)	
Paternal factors			
Paternal Age, yr	32.6 (5.5)	32.7 (5.7)	0.896
Paternal education level			
Low, N (%)	23 (13.4)	14 (16.3)	0.415
Middle, N (%)	60 (34.9)	35 (40.7)	
High, N (%)	89 (51.7)	37 (43.0)	

IVF, In Vitro Fertilization; OHSS, ovarian hyperstimulation syndrome; BMI, body mass index; PCOS, polycystic ovarian syndrome. Data are mean (standard deviation) or number (percent). Maternal and paternal education level were classified as low (middle school or below), middle (high school), and high (college or above). P values were calculated by independent Student t-test, Chi-square test or Fisher's exact test.

Table 3
Intellectual evaluation in offspring.

	Non-OHSS IVF (N = 172)	OHSS (N = 86)	Mean difference (95% CI) Unadjusted	Mean difference (95% CI) Model 1	Mean difference (95% CI) Model 2
Verbal IQ	100.1 (13.2)	92.7 (14.7)	−7.4 (−11.0 to −3.8)	−7.0 (−10.7 to −3.3)	−1.4 (−5.3 to 2.5)
Performance IQ	113.7 (10.8)	108.9 (13.1)	−4.8 (−7.8 to −1.8)	−4.9 (−8.0 to −1.8)	−0.6 (−4.0 to 2.7)
Full IQ	107.4 (11.5)	100.6 (13.4)	−6.8 (−9.9 to −3.6)	−6.6 (−9.9 to −3.3)	−1.3 (−4.7 to 2.1)

Data are mean (SD), or mean difference (95% confidence interval). Model 1 adjusted for child age, gestational age, birth weight, maternal age, nulliparous, maternal PCOS, maternal education, paternal age, paternal education, gestational diabetes, preeclampsia, intrahepatic cholestasis of pregnancy, apgar score < 7 and respiratory distress syndrome. Model 2 additionally adjusted for maternal estradiol level on the day of hCG administration.

value of maternal estradiol level on hCG administration day of non-OHSS IVF group (13,723 pmol/L). The mean estradiol level of each subgroup were 10,653 pmol/L (non-OHSS IVF Low E_2),16,501 pmol/L (non-OHSS IVF High E_2), 11,382 pmol/L (OHSS Low E_2), and 18,571 pmol/L (OHSS High E_2). FIQ of high estradiol non-OHSS subgroup was lower compared with low estradiol non-OHSS subgroup. FIQ of high estradiol OHSS subgroup was also lower compared with low estradiol OHSS subgroup. FIQ of low estradiol non-OHSS and low estradiol OHSS subgroup were also similar (Fig. 2).

To further investigate the relationship between maternal serum estradiol level on hCG administration day and intellectual development of offspring, we performed a linear correlation analysis. The logarithm of maternal serum estradiol level on hCG administration day were negatively correlated with FIQ in OHSS and non-OHSS children (r = −0.424, p < 0.001) (Fig. 3).

4. Discussion

The increasing use of ARTs has helped millions of infertile couples to have children. The long-term safety of ARTs offspring is drawing much attention recently, but little is known about how OHSS will affect offspring. Here, we showed that children born to OHSS women displayed reduced intellectual ability. This problem does not appear to be related to parental factors or the ARTs procedure, but to abnormal hormonal change.

The intellectual ability testing tool we used, C-WISC, is the Chinese version of WISC-III. It is widely used for intellectual assessment for children from 3 to 7 (Moura et al., 2014). The main parameters of the C-WISC (VIQ, PIQ, and FIQ) represent the speech, performance, and overall intelligence levels, respectively. The OHSS children manifested reduced function in both speech and performance, especially speech.

The study also provided information on potential mechanism. The reduced intellectual ability might come from parental predisposing factors, embryo manipulation during IVF and hormonal effects. Parent-related factors such as concomitant diseases, parental age, or parental education level could be responsible for long-term health problems in the offspring. However, it's unlikely the case in this study. The parental age and education level were similar between the groups. Embryo manipulation during IVF is probably not the reason neither. All OHSS cases in this study underwent IVF, just as the non-OHSS cases. Therefore, we proposed that hormonal effects are the main reason for the reduced intellectual ability.

OHSS is a complex syndrome involving multiple factors, such as drastic hormonal change, fluid shift, blood volume depletion. Estradiol elevation is one of the main factors in pathogenesis of OHSS. We have

previously showed cardiovascular dysfunction in OHSS children, and following analysis based on proteomics of OHSS umbilical vessels suggested the role of estradiol in it (Xu et al., 2014). In this study, difference of FIQ became insignificant when maternal estradiol level on hCG administration day was added as covariates in model 2. This result indicated that maternal estradiol level is associated with offspring IQ. We further set subgroups divided by estradiol levels, and find reduced FIQ in OHSS high estradiol subgroup, of which mean estradiol concentration on hCG administration day was over 18,000 pmol/L. And correlation analysis also indicated the negative impact of estradiol on offspring IQ. We proposed that estradiol exerted adverse neurological effects when its concentration was above a certain threshold.

However, some other hormones other than estradiol, such as vascular endothelial growth factor and the renin-angiotensin-aldosterone system, which we were not able to test in the study, might also be responsible for the problems in OHSS offspring. Estradiol might not be the only reason for that. Further studies on the other mechanism are required.

There are several limitations and considerations with regard to the present study. Firstly, some parental information, such as social class and income, was not obtained. Although we included parental education information into the study, social class and income, other factors, which were not included, might be influencing factors. Secondly, the evaluated children were 4 to 7 years old and their intelligence levels were still in the rapid development stage. In order to confirm whether the reduction of intellectual ability will persist in adult life, it is necessary to make a longer follow-up.
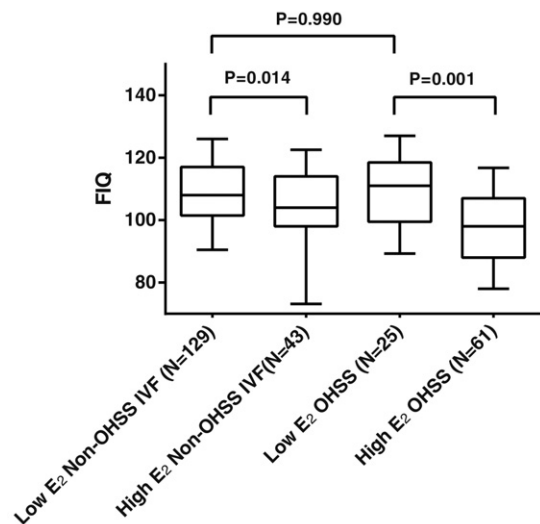
Table 4
The prevalence of low IQ (<80) children.

Characteristic		Non-OHSS IVF (N = 172)	OHSS (N = 86)	P value
Verbal IQ	<80	12 (7.0%)	17 (19.8%)	<0.001
Performance IQ	<80	0 (0.0%)	4 (4.7%)	0.012
Full IQ	<80	3 (1.7%)	7 (8.1%)	0.012

Data are shown as N (%). P values were calculated using Chi-square test or Fisher's exact test.

Fig. 2. FIQ of high and low estradiol subgroup in non-OHSS IVF and OHSS offspring. Both non-OHSS IVF group and OHSS group were divided into low E2 and high E2 subgroup by the 75th percentile value of maternal estradiol level on hCG administration day of non-OHSS IVF group (13,723 pmol/L). The boxes extend from the 25th to 75th percentiles. Whiskers indicate the 5 and 95 percentiles. The lines in the middle of the boxes are plotted at the median value. P values were calculated by ANOVA with Turkey post-hoc analysis. E2, Estradiol. FIQ, full intelligence quotient.
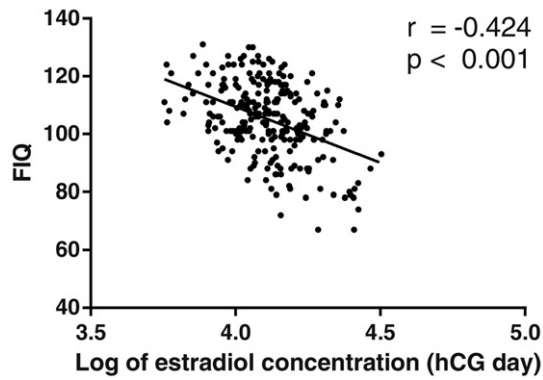
Fig. 3. Correlation between maternal serum estradiol levels on hCG administration day and IQ scores in non-OHSS IVF and OHSS offspring (N = 258). Negative linear correlation between maternal serum estradiol levels on hCG administration day and FIQ. FIQ, full intelligence quotient.

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Conflicts of Interest

The author(s) declare no competing financial interests.

Author Contributions

Gu-Feng Xu and Cheng-Liang Zhou analyzed the data and wrote this manuscript, Yi-Meng Xiong, Jing-Yi Li, Tian-Tian Yu, Shen Tian, Xian-Hua Lin, Yun Liao, Yuan Lv, Fang-Hong Zhang, Zhi-Wei Liu, Yin-Yin Shi, Yan Shen and Jin Sha enrolled the participants, reviewed the information of participants and performed the intelligence tests, Dan Zhang prepared the figures, Yi-Min Zhu, Jian-Zhong Sheng and He-Feng Huang designed the cohort study.

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