

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Obstetrics and Gynecology

**Manuscript NO:** 35878

**Title:** Observed prevalence and risk factors of Birth defects in Shanghai ,China

**Reviewer's code:** 00742121

**Reviewer's country:** Greece

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-08-24

**Date reviewed:** 2017-08-31

**Review time:** 6 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input checked="" type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

## COMMENTS TO AUTHORS

This is an interesting paper worthy of publication after major revision according to the following comments: - The paper contains multiple linguistic and typing errors (many of such errors have been noted in the attached "Manuscript with comments"). Hence, an expert in English should review the paper. - Introduction and Discussion (p.8): The authors should briefly describe how prenatal screening is conducted in their hospital or the study population, including information on first trimester ultrasound scan, anomaly scan, growth scan, chorionic villous sampling and amniocentesis, screening for gestational diabetes and hypertensive disorders etc. It is also very important to report the rate of induced termination of pregnancy due to prenatally diagnosed fetal anomalies, as this would definitely alter the prevalence of defects diagnosed postnatally. - Results and Discussion (p.9): The authors should report the overall ratio of male to female infants among the total of 82,814 births and how this might have influenced the

findings of this study. - Discussion, p.8: How do the authors explain the different incidence of birth defects between Sanghai and the rest of China? Are there any differences in prenatal screening leading to more terminations of pregnancy in Sanghai? - Discussion, p. 9: The authors should provide more details regarding the possible association between ICSI and certain anomalies. - Discussion, p. 10-11: The authors should discuss whether the differences found between permanent residents and migrants were due to possible temporary moving to Sanghai only in order to give birth in a tertiary center rather than in a rural hospital. - Discussion, p.12, last paragraph: The authors should me more precise regarding future measures that should be taken regarding prenatal screening and migrant care.

#### Answers

1. Introduction and Discussion (p.8): The authors should briefly describe how prenatal screening is conducted in their hospital or the study population, including information on first trimester ultrasound scan, anomaly scan, growth scan, chorionic villous sampling and amniocentesis, screening for gestational diabetes and hypertensive disorders etc. It is also very important to report the rate of induced termination of pregnancy due to prenatally diagnosed fetal anomalies, as this would definitely alter the prevalence of defects diagnosed postnatally.

Our hospital regularly monitors women with gestational diabetes and hypertensive disorders. Our hospital also focuses on screening for major malformations during the first trimester by ultrasound and the monitoring of fetal growth to find potential anomalies. Additionally, the use of invasive prenatal diagnostic techniques including amniocentesis, chorionic villus sampling (CVS), fetal blood sampling and embryoscopy, help in the identification of anomalies.

I try to acquire the rate of induced termination of pregnancy in our hospital due to prenatally diagnosed fetal anomalies , but this data was unavailable.

2. The authors should report the overall ratio of male to female infants among the total of 82,814 births and how this might have influenced the findings of this study.

There were 42829 male infants ( 51.7%) and 39990 females ( 48.3%), and the overall ratio of male to female infants was 1.07 : 1. So the birth defects of male infants may account more in the whole population.

3. Discussion, p.8: How do the authors explain the different incidence of birth defects between Shanghai and the rest of China?

The incidence of birth defects in eastern areas was higher than that in middle and western areas within China in 2014. Pregnant women in Shanghai regularly participate in prenatal screenings and are likely to maintain the pregnancy unless serious diseases such as very severe heart defects and multiple

malformations are present, which leads to fewer terminations of pregnancy in Shanghai than in other areas.

4. Discussion, p. 9: The authors should provide more details regarding the possible association between ICSI and certain anomalies.  
Compared with births after spontaneous conception, births resulting from IVF and ICSI combined were found to be associated with a significantly increased risk of any birth defect (unadjusted odds ratio, 1.43; 95% CI, 1.26-1.62)<sup>[11]</sup>
5. Discussion, p. 10-11: The authors should discuss whether the differences found between permanent residents and migrants were due to possible temporary moving to Shanghai only in order to give birth in a tertiary center rather than in a rural hospital.  
The severe perinatal complications in most migrant women were possibly due to their temporary move to Shanghai in order to give birth at a tertiary center, rather than at a rural hospital, where it is safer for mothers and fetuses.
6. Discussion, p.12, last paragraph: The authors should be more precise regarding future measures that should be taken regarding prenatal screening and migrant care.  
Based on this result, the recommended interventions are as follows: 1) regular screening tests among pregnant women are needed at local health care sectors in Shanghai, and 2) despite the difficulty, the primary emphasis should be to enhance the management (provide more knowledge and training for pregnant women during the prenatal period) and health care (such as folic acid supplementation) of women in migrant populations in the future.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Obstetrics and Gynecology

**Manuscript NO:** 35878

**Title:** Observed prevalence and risk factors of Birth defects in Shanghai ,China

**Reviewer's code:** 00742116

**Reviewer's country:** Greece

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-08-24

**Date reviewed:** 2017-09-03

**Review time:** 10 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

## COMMENTS TO AUTHORS

**GENERAL COMMENTS** The Authors present observed prevalence and risk factors of birth defects in Shanghai, China. The manuscript needs review by a proofreader with good written English skills as several syntax errors are present misleading the reader. Furthermore, Discussion section needs improvement, being more concise and providing evidence (references) of bibliographic data presented to support findings of the study...

**SPECIFIC COMMENTS** In both the text and the tables, two types of birth or delivery are presented i.e. cesarean section or delivery and natural birth or delivery. It would be better to rephrase "natural birth", which in fact means delivery without any medication for induction or augmentation, to "vaginal delivery", the latter including normal vaginal delivery (in which natural birth is included) and assisted vaginal delivery (vacuum extraction and forceps delivery). **ABSTRACT Results** Rephrase "twins or multifetal pregnancies" "twins or higher order multiple pregnancies" given that

twins are multiple (or multifetal) pregnancies as well... Core Tip "OFC" stands for "orofacial clefts"... its should be explained when is first mentioned din the text...

**MATERIALS & METHODS** The Authors state "The anomalies were diagnosed prenatally, at birth or 7 days after delivery, including all live births, stillbirths and terminations of pregnancy. If the gestational age at birth was unknown, infants of body weight greater than 1000g were monitored". However, not a certain gestational age above which monitoring was conducted is mentioned in Materials & Methods, but in the discussion it is stated "Secondly, the prevalence did not cover births <28 weeks of gestation.", talking about possible drawbacks of the study! It is imperative that it is clarified in the section Materials & Methods as it is well known that according to the National hospital-based system running in China over the past 25 years, the birth population includes fetus or neonates with 28 gestation weeks or more who are born in hospitals within the surveillance system including live births, stillbirths and legal pregnancy termination. The Authors should explain how were multiple birth defects concurrently present in a neonate were analyzed in the study The Authors state "An interview was conducted for mother or father...". However, it is crucial that the mother is interviewed especially regarding potential embryotoxic effects during the first trimester of pregnancy, as the father may be not informed about such a behavior.

**DISCUSSION** The Authors state "The prevalence of polydactyly/syndactyly, hypospadias, cleft lip and palate and accessory auricle anomalies grew in our study. This may be caused by environmental factors or intracytoplasmic sperm injection". Is there any proof that ICSI increasingly performed in infertile couples in the area studied? One could hypothesize that birth defects showing a decrease in prevalence in this study may be attributed in the increasing expertise of sonographers diagnosing more and more fetal anomalies as well as increasing adherence of pregnant women of prenatal screening in this area. Are there any data regarding these issues? Given that the Authors state that "Early intervention such as induced abortions would be taken of neural tube defects was detected by clinical and ultrasound data", the aforementioned hypothesis may turn out to be valid. The Authors should provide a reference for the statement "Earlier abortions of female may affect potentially the sex ratio. Combined with the one-child policy, traditional preference for male infants in China resulted in widespread abortions of female (especially for severe congenital heart disease, cleft lip, etc)." The Authors state "In migrant population, high risk pregnancy factors, such as older mothers, too young mother (maternal age<20 years) and pregnancy-related problems may lead to miscarriage, preterm or low birth weight of infant". However, data proving this statement are not presented in the study... **TABLES** Table 1 and Table 2 can be merged in one Table. Furthermore, in Table 1 the amount of birth defects presented each year should be accompanied by the number of births conducted each year.



**Baishideng  
Publishing  
Group**

7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** bpgoffice@wjgnet.com  
**https://** www.wjgnet.com

## Answers

1. I have rephrased “natural birth” to “vaginal delivery” in my manuscript.
2. **ABSTRACT:** I have rephrased “twins or multifetal pregnancies” to “twin births or higher order multiple pregnancies”; Core Tip “OFCs” stands for “orofacial clefts”
3. **Materials & Methods:**

I have added “According to the national hospital-based system that has been administered in China for more than 25 years, the birth population includes fetuses and neonates at 28 weeks or more of gestation, including live births and still births, who are born in hospitals within the surveillance system”

I rephrased “An interview was conducted for mother or father...” to “An interview of the mothers was conducted”

The incidence of multiple birth defects concurrently present in a neonate in the study was 7.3%(60/824).
4. **DISCUSSION:** Is there any proof that ICSI increasingly performed in infertile couples in the area studied?

Since the time the first infant was born as a result of ART in China in 1988, more and more infants have been born after use of ART<sup>[10]</sup>. Compared with births after spontaneous conception, births resulting from IVF and ICSI combined were found to be associated with a significantly increased risk of any birth defect (unadjusted odds ratio, 1.43; 95% CI, 1.26-1.62)<sup>[11]</sup>
5. The Authors should provide a reference for the statement “Earlier abortions of female may affect potentially the sex ratio. Combined with the one-child policy, traditional preference for male infants in China resulted in widespread abortions of female”

Therefore, the birth defects in male infants may account for more in the whole population. This may be due to differences in hormone levels or because the Y chromosome has a higher susceptibility to damage than the X chromosome<sup>[15]</sup>. In addition, external genital deformities in females were less likely to be found than those in males. However, earlier abortions of female fetuses may have affected the sex ratio. Combined with the one-child policy, the traditional preference for male infants in China has resulted in widespread abortions of female fetuses<sup>[16]</sup>.
6. The Authors state “In migrant population, high risk pregnancy factors, such as older

mothers, too young mother (maternal age<20 years) and pregnancy-related problems may lead to miscarriage, preterm or low birth weight of infant". However, data proving this statement are not presented in the study...

The current study reported that permanent residents have a lower risk of birth defects, but this finding requires further investigation of the influence of genetic, cultural and environmental factors on birth defects. In the entire migrant population, the proportion of women aged <20, ≥20 but <25, ≥25 but <35 and ≥35 but <40 and ≥40 was 1.0%, 14.9%, 9.5%, and 2.0%, respectively, which was higher than the corresponding proportion of all permanent residents in these age groups (0.2%, 7.7%, 6.9%, 1.0%, respectively).

I deleted "pregnancy-related problems may lead to miscarriage, preterm or low birth weight of infant"

7. TABLES I have merged table 1 and table 2 in one Table.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Obstetrics and Gynecology

**Manuscript NO:** 35878

**Title:** Observed prevalence and risk factors of Birth defects in Shanghai ,China

**Reviewer's code:** 00742268

**Reviewer's country:** Saudi Arabia

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-08-24

**Date reviewed:** 2017-09-07

**Review time:** 14 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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**Baishideng  
Publishing  
Group**

7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** bpgoffice@wjgnet.com  
**https://** www.wjgnet.com

<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

## COMMENTS TO AUTHORS

The research team report on the prevalence of birth defects in Shanghai in the period 2008-2014. They found that multiple gestation, premature, lower birth weight, twins or multifetal pregnancies cesarean delivery, and migrant population are independent factors of birth defects. Comments Instead of the comment 'Supported by none' the researchers should consider to include an Acknowledgement to recognize those which have contributed with data sets or in another way to the study. Reference 1 and the statement based on it are out of date. If data are available, it would be of interest to know if the cases with birth defects have a recurrent prevalence. It would be of interest to know if adequate data are available from Funshu Hospital:...or intracytoplasmic sperm injection[9]. English language, spelling and scientific editing P2, should consider to use capital letter: Department of neonatology P2:...medical record system... more gestation: multiple gestation chromosomal disease, consider to use: chromosomal disorder, or, chromosomal abnormalities P5,...occured.....occurring... P6: examined P8, needs a clear attribution: ...which was in line with Shanghai. P9,...which were higher than that Inner Mongolia:...which was higher than in Inner Mongolia P9, needs scientific editing:...or Y chromosome had a high susceptibility than X chromosome. P9. probably meant: In addition, external genital deformities in female were less likely to be found than in male. P10: pregnancy P10, needs scientific editing:...and ovarian function and egg quality of women above 35 years old was bad. P11: For example, the use of... P12: interventions are recommended

### Answers

1. Reference 1 and the statement based on it are out of date.  
I removed the reference 1 and the statement based on it.
2. P2, I choose to use capital letter: Department of Neonatology.



**Baishideng  
Publishing  
Group**

7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** bpgoffice@wjgnet.com  
**https://** www.wjgnet.com

3. P2:...medical record system... more gestation: multiple gestation chromosomal disease, I rephrased "chromosomal disease" to "chromosomal disorders" or " chromosomal abnormalities".

P5: I rephrased "occurred" to " occur "

P6: I rephrased "examined" to " assessed ".

P9: I rephrased "...which were higher than that Inner Mongolia" to "which was higher than in Inner Mongolia"

P8, needs a clear attribution: ...which was in line with Shanghai.

I rephrased "...which was in line with Shanghai" to "... which was in agreement with the overall rate in Shanghai" and I added the reference 6.

P9 Y chromosome had a high susceptibility than X chromosome.

Please see reference 15. And I deleted "for instance X chromosome linked recessive inheritance resulting in dominant exhibition in male"

P10."..and ovarian function and egg quality of women above 35 years old was bad."

I rephrased "..and ovarian function and egg quality of women above 35 years old was bad." to "ovarian function and egg quality in women older than 35 years were poor"

P11 I rephrased " For example, the use of multivitamin supplements may be not sufficiently promoted during pregnancy in migrant population" to " the benefits of multivitamin supplements during pregnancy may be insufficiently promoted among migrant populations"

P12 I rephrased " interventions are recommended ..." to " the recommended interventions are as follows..."

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Obstetrics and Gynecology

**Manuscript NO:** 35878

**Title:** Observed prevalence and risk factors of Birth defects in Shanghai ,China

**Reviewer's code:** 00742054

**Reviewer's country:** Australia

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-08-24

**Date reviewed:** 2017-09-08

**Review time:** 14 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input checked="" type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

## COMMENTS TO AUTHORS

Thank you for this interesting and important study! Below are my comments: -Abstract: Methods: please remove the last sentence "Examining the prevalence .... Future intervention". It doesn't belong to this section. Results: please do not use digits at the beginning of the sentence. Instead of "82814 births including ..." you may write "A total of 82814 births including ... ." -I am a bit confused at to whether or not the results include abortion due to fetal defects. In the 'Materials and Methods' section, it has been mentioned that "The anomalies were diagnosed prenatally, at birth or 7 days after delivery, including all live births, stillbirths and terminations of pregnancy." In the 'Results' section, it says "From 2008 to 2014, 82576 live births and 238 stillbirths or abortions were recorded". This means that the numbers provided in Table 2 include live birth, stillbirths and abortion. In 'Discussion' section it says "the prevalence did not cover births <28 weeks of gestation." Since the word "abortion" is defined as

pregnancy termination before 20th week of pregnancy, it is not clear whether pregnancy terminations before 20th gestational week were included in the study. Please clarify and amend the manuscript accordingly. Also Table 3 has two groups of gestational age: “≥37wk” or “<37wks”. Since “< 37 wks” can imply to any time from 0-37 weeks, please clarify exactly what were the gestational age of the fetuses/infants in this study. For example, 28-37 weeks.... -The authors need to be careful with interpretation of the findings. I see there is a statistically significant difference between permanent residents and migrant population in terms of maternal age [“The mean age of women from permanent resident at childbirth was 29.05±3.63 years old, which was significantly higher than that migrant population of 28.90±4.54 years old (t = 3.58, P< 0.001)”]. However, these differences are not clinically significant and no evidence in the literature shows that maternal and neonatal outcome is different between women with mean age 28 and 29. This is supported by the results of logistic regression (Table 3). -It would be useful and interesting to see the results of chi-square test and the difference between healthy babies and those with birth defects in terms of all variables (such as demographics, obstetrics history, birth outcomes, etc.)

Answers:

1. Abstract: Methods: I removed the last sentence “Examining the prevalence .... Future intervention”  
Results: I rephrased “82814 births including ...” to “A total of 82,814 births, including ...”

2. I am a bit confused at to whether or not the results include abortion due to fetal defects.

The results in my study does not include abortion due to fetal defects. In the ‘Materials and Methods’ section, I rephrased “The anomalies were diagnosed prenatally, at birth or 7 days after delivery, including all live births, stillbirths and terminations of pregnancy” to “The anomalies were diagnosed prenatally, at birth or 7 days after delivery. According to the national hospital-based system that has been administered in China for more than 25 years, the birth population includes fetuses and neonates at 28 weeks or more of gestation, including live births and still births, who are born in hospitals within the surveillance system<sup>[3,4]</sup>.”

In the ‘Results’ section, I rephrased “From 2008 to 2014, 82576 live births and 238 stillbirths or abortions were recorded” to “From 2008 to 2014, 82576 live births and 238 stillbirths were recorded” .

3. In table 3 I rephrased gestational age: “<37wks” to “28-37 wks”

4. It would be useful and interesting to see the results of chi-square test and the difference between healthy babies and those with birth defects in terms of all variables (such as demographics, obstetrics history, birth outcomes, etc.)

I am sorry I do not have obstetrics history, birth outcomes of all the healthy babies and those with birth defects in my study, I have the information of the demographics of the infants, and I think I will discuss the

issue in my next study. So I displayed the databases as follows.

Table 3 Neonatal Demographic Findings in Infants With Birth defects and Controls

variables	Birth defects(n=824)	Controls(n=81990)	P-value
Maternal age (years)			0.011
<20	2 (0.2)	272 (0.3)	
20-	82 (10.0)	7271 (8.9)	
25-	392 (47.6)	41469 (50.6)	
30-	249 (30.2)	26036 (31.8)	
35-	74 (9.0)	6006(7.3)	
40-	20 (2.4)	941 (1.1)	
Gender			<0.001
Male	484 (58.7)	42344(51.6)	
Female	335 (40.7)	39651(48.4)	
Gestational age(weeks)			<0.001
≥37	556 (67.5)	75194 (91.7)	
28-37	263 (31.9)	6801 (8.3)	
Birth weight			<0.001
normal	536 (65.0)	72597 (88.5)	
ELBW&VLBW&LBW	242 (29.4)	4500 (5.5)	
macrosomia	41 (5.0)	4898 (6.0)	
Plurality			<0.001
singletons	691 (83.9)	78749(96.0)	
twins or higher order	128 (15.5)	3246 (4.0)	
multiple pregnancies			
Household registration			<0.001
permanent population	617 (74.9)	68313 (83.3)	
migrant population	202 (24.5)	13682 (16.7)	
Delivery mode			<0.001
vaginal delivery	291(35.3)	37945(46.3)	
cesarean delivery	528(64.1)	44050(53.7)	