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Paternal exposure to medical-related radiation associated with low birthweight infants

A large population-based, retrospective cohort study in rural China

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Abstract

Low birthweight (LBW) is closely associated with fetal and perinatal mortality and morbidity. We identified the risk factors of LBW and geographical differences in LBW incidence in 30 Chinese provinces in the present study.

Our main risk factor for LBW is paternal exposure to radiation (odds ratio = 1.537), which has never been studied before.

Abbreviations: BMI = body mass index, CIs = confidence intervals, CT = computed tomography, LBW = low birthweight, NBW = normal birthweight, NPCP = National Pre-pregnancy Checkups Project, ORs = odds ratios, PET-CT = positron emission tomography-computed tomography.

Keywords: incidence, low birthweight infants, paternal exposure to radiation, risk factors

1. Introduction

Weight is an important indicator of infant health, and the mortality rate in low-weight infants is 40 times that of normal-weight infants.1 According to the 2011 United Nations International Children’s Emergency Fund report, an estimated 20 million low-birthweight (LBW) infants are born annually in developing countries, and LBW remains a significant public health problem in many developing countries. According to a study by Yi Chen et al, the incidence of LBW in mainland China was about 6.1%.2 LBW infants are likely to have a high risk of infections, hospitalization, and physiological illness.3 Further, they are more likely to develop atherosclerosis, hypertension, coronary artery disease, and chronic kidney disease later in life.4–9 To lower the incidence of birth defects and improve the overall health of the population in China, the present study focused on the incidence and risk factors of LBW. Although similar studies of LBW have been performed in China, these studies seldom focus on the incidence of LBW because of the limited scope of population and most of them neglect the effects of paternal factors on LBW. Previous studies found some evidences that paternal risk factors can affect the offspring’s physical characteristics and cause some diseases. A study of Bailey et al has shown that fathers who underwent more than one abdominal x-rays were more likely to give birth to children with acute lymphoblastic leukemia.10 Other studies have proved that perceptional paternal exposure to radiation will cause the

Note: This study was a population-based, retrospective cohort study performed in 30 Chinese provinces. We used data from the free National Pre-pregnancy Checkups Project, which is a countrywide population-based retrospective cohort study. To identify regional differences in LBW incidence, we used the Qinling-Huaihe climate line to divide China into northern and southern sections and the Hetai-Tengchong economic line to divide it into eastern and western sections. Multivariate unconditional logistic regression analysis with SAS 9.4 was used for data analysis. P < .05 was considered statistically significant.

LBW incidence was 4.54% in rural China. Southern China had a significantly higher incidence (4.65%) than northern China (4.28%). Our main risk factor for LBW is paternal exposure to radiation (odds ratio = 1.537), which has never been studied before.

This study identifies multiple risk factors of couples giving birth to LBW babies including paternal risk factors.

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occurrence of other cancers like renal cancer and chondrosarcoma.[11] With the development of the medical technology, a report of United States indicated that the exposure to radiation has doubled during the past 3 decades, especially the medical radiation which is considered as small doses of radiation[12,13]; the link between medical radiation and radiation-related hereditary effects remains unclear. So many previous researches have evaluated the health effect of the offspring of atomic bomb survivors, and occupational employees exposed to radiation. However, nobody focused on the relationship between parental pregestational exposure to radiation and LBW. We were the first to include the paternal exposure to medical radiation into our database to investigate whether it was related to LBW. Our study has large sample size since we used national data and received government support. In-depth research on LBW in China is still lacking, so our goal of this study was to identify those at risk for having a LBW baby. These families can focus on reducing their risk factors for LBW during prepregnancy and early pregnancy.

2. Methods

2.1. Data acquisition

The Population and Family Planning Commission collaborated with the Ministry of Finance of China to start the first wave of free pre-pregnancy physical examinations in 60% of the pilot counties in China between January 2010 and December 2012. We used data from childbearing-aged couples who delivered babies from January 2010 to December 2013 in the 31 pilot counties of China. The data used in this study came from the database of the free National Pre-pregnancy Checkups Project (NPNC), which is a population-based, retrospective cohort study of free, preconception medical examinations and services for rural reproductive-age couples who are trying to conceive throughout the 30 provinces of China. By the end of 2013, 11.42 million families had participated in this project and they had given birth to a total of 248,501 babies. We included 192,492 records with complete weight information in this study and they had given birth to a total of 248,501 babies. We included 192,492 records with complete weight information for single live babies in this study (Fig. 1). We have gained ethics approval with the ethics committee of Chinese Academy Medical School and Peking Union Medical College Hospital (the reference number: S-K132). We have also obtained the consent to participate from the participant by signing informed consent forms (Chinese Edition) before they filled in the questionnaire. Stress statues and gum bleeding were recorded by the interviewers during the previous 3 months, which divides China into east and west regions based on the Qinling-Huaihe line, which bisects China into North and South regions based on climate and the Helihe-Tengchong line, which divides China into east and west regions based on economic development. Eastern China is more economically developed than western China as most of its cities are coastal cities (Fig. 2).

2.2. Data processing

2.2.1. Diagnosis and assignment to the LBW group. According to a manual published by the World Health Organization, LBW means a birthweight <2500g.[12] As a result, infants’ weights were divided into 2 groups: a LBW (<2500g) and a normal weight (2500~4000g) group.

2.2.2. Variable grouping, assignment and definitions of variables. The data of exposure to radiation in the residence before pregnancy, which may indicate the exposure of x-ray, computed tomography (CT), positron emission tomography-computed tomography(PET-CT) or other radionuclide imaging before pregnancy, were obtained by a “yes or no” question, namely “If any x-ray, CT, PET-CT or other radionuclide imaging was underwent in your residence or workplace within 6 months before you got pregnant?” All the mothers/fathers whose answers to this question were “yes” would be grouped as “exposed”, and the rest ones were defined as “non-exposed.” Oral contraception use means that mothers have used it within 6 months before pregnancy as well. We also asked the mothers to answer whether they take folic acid regularly within 1 month before pregnancy and during the previous 3 months, “Irregular” refers “No” in their answers. Stress statues and gum bleeding were recorded by their answers to “Do you feel stressed?” “Do you usually have gum bleeding?” on questionnaire as well. “Yes” means “Having stress” and “Having gum bleeding”, “No” means “Not having stress” and “No gum bleeding.” Table 2 shows how the variables were assigned to groups. In the table, “♂” means father of the baby and “♀” means mother. Chinese body mass index (BMI) classification standards were used in this study to classify different BMI groups.[13]

2.2.3. Description of region designation. The 30 provinces included in the study were: Beijing, Hebei, Jiangsu, Anhui, Jilin, Zhejiang, Fujian, Jiangxi, Henan, Hubei, Guangdong, Sichuan, Chongqing, Yunnan, Shanxi, Tianjin, Shanghai, Guangxi, Hunan, Shandong, Hainan, Heilongjiang, Qinghai, Tibet, Inner Mongolia, Shanxi, Liaoning, Ningxia, Guizhou, and Gansu. In this study, we divided China geographically into 4 regions with the Qinling-Huaihe line, which bisects China into North and South regions based on climate and the Helihe-Tengchong line, which divides China into east and west regions based on economic development.
2.2.4. Statistical analyses. In our study, LBW was a dependent variable. In single-factor analysis, the \( \chi^2 \) test was used to analyze qualitative data, the independent sample \( t \) test and 1-way analysis of variance were used for quantitative data analysis. We also calculated the Spearman rank correlation coefficient for correlation analyses. Stepwise multivariate logistic regression was performed in multifactor analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by use of both univariate and multivariate analyses. \( P < .05 \) was considered statistically significant. SAS 9.4 statistical packages were used for data analysis.

3. Results

Of the 192,492 infants in our study, 9,275 of them were LBW with a mean weight of 2088.8±407.4g. There were 183,217 infants with a normal birthweight (NBW) and the mean NBW was 3311.3±340.2g (\( P < .001 \)). Our results indicate that the incidence of LBW in mainland rural area of China was 4.54% with south China having a higher incidence of LBW (4.65\% \( P < .001 \)) compared with north China (4.28\%, \( P = .848 \)) (Table 1).

Several factors were found significant by univariate analysis. These factors included: weight (♂, ♀), height (♂, ♀), age of menarche (♀), age (♀), BMI (♀), exposure to poisonous materials and radiation (♀), blood pressure (♂), gum bleeding (♂), stress, use of a contraceptive drugs (♂), folic acid intake (♂), uterine activity, infant’s sex, BMI (♀), and red blood cell count (♂) ("♂" means man, "♀" means woman) (Table 2). Factors found significant by multivariate analysis which were adjusted for age, occupation, education, sex of baby, parity were: hypertension (odds ratio [OR]=2.326, [1.349,4.013]), paternal exposure to radiation (OR=1.537, [1.083,2.181]), contraceptive drug use (OR=2.318, [1.059,5.074]), both parents with stress (OR=1.146, [1.047,1.255]), irregular use of folic acid (OR=1.121, [1.001,1.255]), maternal BMI <24 (OR=1.113, [1.030,1.202]) (Fig. 3). Table 3 showed the comparison of both paternal and neonatal characteristics between fathers exposed to radiation and unexposed to radiation. The average infant birthweight in the group of fathers exposed to radiation was 3239.5 g, whereas it was 3252.5g in the population who wa not exposed to radiation (\( P = .032 \)). Additionally, fathers who were exposed to radiation were likely to give birth to premature infants (\( P = .006 \)).

4. Discussion

LBW is common worldwide, especially in developing countries. The percent of LBW in developing countries is far higher than in developed countries.\[14,15\] Therefore, it is especially important to find as many as risk factors of LBW. The data for this study came from the free NPCP. Our study had a large number of samples and this kind of large sample research has not happened in previous studies. Our data indicated that the incidence of LBW in China was 4.54\% with south China having a higher incidence of LBW (4.65\%) compared with north China (4.28\%, \( P < .001 \)). There were little differences between the distribution of LBW incidences in eastern (4.42\%, \( P = .848 \)) and western China (4.42\%, \( P = .848 \)) (Table 1).

Several factors were found significant by univariate analysis. These factors included: weight (♂, ♀), height (♂, ♀), age of menarche (♀), age (♀), BMI (♀), exposure to poisonous materials and radiation (♀), blood pressure (♂), gum bleeding (♂), stress, use of a contraceptive drugs (♂), folic acid intake (♂), uterine activity, infant’s sex, BMI (♀), and red blood cell count (♂) ("♂" means man, "♀" means woman) (Table 2). Factors found significant by multivariate analysis which were adjusted for age, occupation, education, sex of baby, parity were: hypertension (odds ratio [OR]=2.326, [1.349,4.013]), paternal exposure to radiation (OR=1.537, [1.083,2.181]), contraceptive drug use (OR=2.318, [1.059,5.074]), both parents with stress (OR=1.146, [1.047,1.255]), irregular use of folic acid (OR=1.121, [1.001,1.255]), maternal BMI <24 (OR=1.113, [1.030,1.202]) (Fig. 3). Table 3 showed the comparison of both paternal and neonatal characteristics between fathers exposed to radiation and unexposed to radiation. The average infant birthweight in the group of fathers exposed to radiation was 3239.5 g, whereas it was 3252.5g in the population who wa not exposed to radiation (\( P = .032 \)). Additionally, fathers who were exposed to radiation were likely to give birth to premature infants (\( P = .006 \)).

<table>
<thead>
<tr>
<th>Area</th>
<th>NBW, N (%)</th>
<th>LBW, N (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>53,370 (95.42%)</td>
<td>2,563 (4.58%)</td>
<td>1.0761 (1.0270, 1.1275)</td>
</tr>
<tr>
<td>South</td>
<td>128,663 (95.09%)</td>
<td>6,649 (4.91%)</td>
<td>1.0381 (1.0039, 1.0739)</td>
</tr>
<tr>
<td>East</td>
<td>174,621 (95.17%)</td>
<td>8,854 (4.83%)</td>
<td>1.0761 (1.0270, 1.1275)</td>
</tr>
<tr>
<td>West</td>
<td>7,823 (95.31%)</td>
<td>385 (4.59%)</td>
<td>1.0381 (1.0039, 1.0739)</td>
</tr>
</tbody>
</table>

NBW=low birthweight, NBW=normal birthweight.
rural areas of China was 4.54%. Southern China had a higher incidence of LBW ($P < .05$). There were no significant differences in LBW between eastern and western China. Climate and eating habits may play a critical role in the reason for the regional differences and similarities. People in the north are generally taller and heavier than those in the south, and the winter is much colder in the north than in the south. Therefore, people living in the north have diet that is high in calories; it may be the reason for the lower incidence of LBW in north.

Among the studies of LBW worldwide, the significant maternal risk factors for LBW contained abnormal weight gain during pregnancy, low family functioning, stressful events, cigarette smoking, a previous preterm or LBW baby, anemia, and having a pregnancy, low family functioning, stressful events, cigarette smoking, a previous preterm or LBW baby, anemia, and having a

In our study, we found the following to be significant risk factors for LBW (using multivariate analysis): paternal exposure to radiation, hypertension, use of contraceptive drugs, presence of pressure in both parents, irregular use of folic acid, and maternal BMI $< 2.4$ kg/m$^2$.

It is generally known that maternal exposure to radiation before pregnancy can increase the possibility of fetal malformations including LBW. However, our results indicated that paternal history of exposing to radiation (OR = 1.329) was related to LBW and nobody has reported a relationship between paternal radiation exposure and LBW. Human studies showed that fathers who were exposed to the nuclear plant or medical radiation were prone to give birth to children with leukemia or defect. Recent studies proved that paternal exposure to radiation could cause gene instability, especially for those cancer-related genes. Many such genes suppressed or overexpressed in the next generations of irradiated mice 23. Another animal experiment showed that paternal irradiation would disturb the expression of circadian genes in offspring. They found that gene involved in the rhythmic process overpresented in irradiated male mice 24. Besides, transgenerational instability of the next generation was
observed in Mughal et al’ study because of a threshold dose of acute paternal irradiation. But the reasons why paternal exposure to radiation was associated with LBW still needs further study. We hypothesize that the similar mechanism may act during the process of LBW formation. Several studies have been carried out on the gene etiology of LBW. Among them, Buschdorf et al’s study found that gene expressed on hippocampal participated in the promotor area of HUSB and finally detected low level of methylation in this study because of a threshold dose of acute paternal irradiation. But the reasons why paternal exposure to radiation and LBW. The relationship between paternal exposure to radiation and LBW. The risk factors for LBW identified in this study are modifiable and preventable. To reduce LBW incidence in China, holistic approaches such as health education, maternal nutrition, improvement in socioeconomic indices, and increasing the quality and quantity of antenatal care services are of paramount importance.

Acknowledgments

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References


Table 4

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Maternal risk factors</th>
<th>Paternal risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bian et al (2013)</td>
<td>55,633</td>
<td>Low primary education, anemia, hypertensive disorders, placental previa, oligohydramnios and premature rupture of membrane, primary education, anemia, and hypertensive disorders</td>
<td>N</td>
</tr>
<tr>
<td>Liu et al (2013)</td>
<td>111,181</td>
<td>Being female infant, preterm delivery, lower educational level of mothers, antenatal care times &lt;4, antenatal care times ≥8, gestational hypertension, being multipara, taking no folic acid during pregnancy</td>
<td>N</td>
</tr>
<tr>
<td>Zhang et al (2002)</td>
<td>999</td>
<td>Multiparity, preterm birth, abnormal maternal health status and maternal malnutrition, maternal medical conditions during pregnancy, maternal schooling</td>
<td>N</td>
</tr>
<tr>
<td>Fan et al (2015)</td>
<td>829</td>
<td>Maternal lower education, lower gestational weight gain, being primipara and shorter gestational age, mothers with the history of chronic disease, women who increased non-staple food consumption. Lifestyle factors including diet, exercise, screen time, drinking and smoking from both maternal and paternal exhibited little influence on fetal birthweight.</td>
<td>Fathers living in the rural area</td>
</tr>
<tr>
<td>Chen et al (2013)</td>
<td>101,163</td>
<td>Maternal age of &lt;20 years, low level of maternal education, previous histories of adverse pregnancies, hypertensive disorders during pregnancy, anemia, oligohydramnios, premature rupture of membranes, and gestational diabetes.</td>
<td>N</td>
</tr>
</tbody>
</table>

5. Conclusions

We showed that the incidence of LBW in rural areas of China is 4.54%, and that south China has a higher incidence of LBW than north China ($P < .05$). Our work is the first to show the relationship between paternal exposure to radiation and LBW. The risk factors for LBW identified in this study are modifiable and preventable. To reduce LBW incidence in China, holistic approaches such as health education, maternal nutrition, improvement in socioeconomic indices, and increasing the quality and quantity of antenatal care services are of paramount importance.


