Association Between Paternal Schizophrenia and Low Birthweight: A Nationwide Population-Based Study

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Using a nationwide population-based dataset, the aim of the present study was to investigate the association between paternal schizophrenia and the risk of low birthweight (LBW). This study linked the 2001 Taiwan National Health Insurance Research Dataset with Taiwan’s birth and death certificate registries. In total, 220 465 singleton live births were included. The key dependent variable was whether or not an infant’s father was diagnosed with schizophrenia, while the independent variable of interest was whether an infant had LBW. Multivariate logistic regression analysis was performed to explore the relationship between paternal schizophrenia and the risk of LBW, after adjusting for the infant and parents’ characteristics. The results show that infants whose fathers had schizophrenia were more likely to have LBW than those whose fathers did not (12.6% vs 8.0%). Infants whose fathers had schizophrenia were found to be 1.58 (95% confidence interval 1.10–2.52, \(P < .05\)) times more likely to have LBW than their counterparts whose fathers did not have schizophrenia, following adjustment for gestational week at birth, parity, paternal age and highest educational level, family monthly incomes, and marital status. We conclude that the offspring whose fathers had a diagnosis of schizophrenia had increased risk of LBW compared with those whose fathers had no schizophrenia. This finding paves the way for further studies and suggests that there may be potential benefit to early intervention to prevent LBW in pregnant women with husbands with schizophrenia.

Key words: schizophrenia/birthweight/paternal schizophrenia

Introduction

Increasing attention has been paid to the effect of paternal characteristics on adverse pregnancy outcomes, particularly infant birthweight, during the past decade.1 A growing number of studies have reported that paternal characteristics such as age, height, weight, race, educational level, and occupation were associated with variation in birthweight, after adjusting for maternal and pregnancy-specific factors.2–8 Some researchers have suggested that because the placenta is largely dependent on the expression of genes of paternal origin,9 it is biologically plausible that fetal growth is influenced by paternal factors. With regard to mental illness, literature reviews reveal that women with schizophrenia have an increased risk of giving birth to low birthweight (LBW) babies, compared with healthy pregnant women.10,11 Still, to the best of our knowledge, few attempts have been made to examine the relationship between paternal mental illness and adverse pregnancy outcomes.

Schizophrenia is considered strongly influenced by genetic inheritance, whether traceable to maternal or paternal schizophrenia. Thus, it seems reasonable to assume that not only children of mothers with schizophrenia but also those with fathers with schizophrenia might be at increased risk of neurodevelopmental impairment. Recently, Webb et al12 published a study on the association between paternal schizophrenia and fatal birth defects. They used the data on all singleton live births in Denmark during 1973–1998 but found no elevation in risk of fatal birth defects relating to paternal schizophrenia. However, their study measured only severely adverse birth outcomes, and a substantial proportion of the paternal data was missing. Such limitations preclude unequivocal acceptance of their findings.

Using a Taiwan nationwide population-based dataset, the aim of the present study is to investigate the association between paternal schizophrenia and the risk of LBW, after adjusting for the characteristics of infant, mother, and father. LBW is associated not only with neurodevelopmental impairment but also with increased risk of mortality and morbidity in infants, as well as adverse long-term consequences for the child.13,14 LBW may be preventable, however.1 Therefore, exploring the association between paternal schizophrenia and the risk of LBW...
might not only help researchers understand the possible genetic or environmental mechanisms linking parental mental illness and fetal birthweight but could also generate opportunities for clinicians to provide specific, optimal prenatal care.

Methods

Database

This study linked 3 large-scaled national databases. First, we used data from the 2001 National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute in Taiwan. The NHIRD includes a registry of contracted medical facilities, a registry of board-certified physicians, a registry of catastrophic illness patients and a monthly summary of inpatient and ambulatory care claims for over 21 million enrollees, representing around 96% of the island’s population. The NHIRD provides one principal diagnosis as identified from death certificates.

The second database used in this study is the birth certificate registry published by the Ministry of Interior in Taiwan. The data on birth certificates include birthdates for both infants and their parents, gestational week at birth, infant birthweight, gender, parity, place of birth, parental educational level, and maternal marital status.

The third database included in this study is death certificate published by the Department of Health in Taiwan; it provides data on all Taiwanese citizens, including marital status, employment status, place of legal residence, date of birth and death, and cause of death (ICD-9-CM code). Because the registration of all births and deaths is mandatory in Taiwan, its birth and death certificate data are considered to be extremely accurate and comprehensive. With assistance from the Bureau of the National Health Insurance (NHI) in Taiwan, the mother’s and infant’s unique personal identification numbers provided links between the NHIRD and birth and death certificate data. All personal identifiers were encrypted by the Bureau of NHI before release to the researchers. The confidentiality assurances were addressed by abiding the data regulations of the Bureau of NHI.

Study Sample

The sample for this research initially comprised all births in Taiwan between January 1, 2001, and December 31, 2001. We excluded multiple deliveries (as such women might have different obstetric considerations different from women with singleton gestations) and stillbirths (infants who died before reaching their first birthday) as identified from death certificates.

Parental mental disorders were identified through the registry of catastrophic illness in the NHIRD. Because this study focuses specifically on paternal schizophrenia (ICD-9-CM code 295), infants whose fathers had mental disorders other than schizophrenia listed in the registry were excluded. We also excluded infants whose mothers had any type of mental disorder listed in the registry of catastrophic illness.

In Taiwan, patients with certain serious mental disorders are issued a catastrophic illness card by the Bureau of NHI to reduce the financial burden of their illness. Psychiatric diseases, ICD-9-CM codes 290 and 293–297 (senile and presenile organic psychotic conditions, transient organic psychotic conditions, other organic psychotic conditions, schizophrenia, affective psychoses, and paranoid states) are included in this registry. Despite a lack of validity studies, psychiatric diagnoses in the catastrophic illness registry may be more reliable than claims data in the NHIRD because the application for a catastrophic illness card must be signed by a board-certificated psychiatrist after the diagnosis is verified through a number of visits. Because copayments for psychiatric care, whether outpatient or inpatient, are waived for catastrophic illness cardholders, the majority of patients with schizophrenia are likely to have applied for the card and to be recorded in the registry.

In addition, we think that this dataset is fairly comprehensive. Although people in Chinese culture traditionally are reluctant to go to psychiatrists in order to avoid the social stigma associated with mental illness, we think schizophrenia is so uniquely disruptive that it is less likely to go completely undiagnosed and untreated than other mental illnesses. At the same time, the stigma associated with receiving mental health care appears to be declining in Taiwan, where the use of antidepressants, eg, skyrocke-ted in the last few years.15

Ultimately, after excluding cases with infant, maternal, or paternal information missing (n = 678), 220 465 singleton live births fulfilled our criteria and were included in our study.

Variables of Interest

The key dependent variable was dichotomous—whether or not an infant’s father had schizophrenia—while the independent variable of interest was LBW. According the World Health Organization, the standard cutoff point for LBW in infants is 2500 g (<2500, ≥2500 g).16

Other possible factors contributing to LBW in infants were selected and adjusted for in the logistic regression model based on a previous study in Taiwan about the association between paternal characteristics and pregnancy/neonate outcomes.17 These factors include characteristics of the infant (gender and parity), mother (age, gestational age, the highest educational level, marital status, and gestational hypertension), father (age and the
highest educational level), and family monthly income (including mothers' and fathers' monthly income). Parental ages were defined as each parent's age, in years, at the time of the infant's birth. Because maternal age and education were highly correlated with paternal age and education (correlation coefficients of 0.616 and 0.523, respectively), they were removed in following analyses.

Variables not normally distributed were grouped into categories mainly following a previous study. Age was grouped into 3 categories, with comparable numbers of paternal schizophrenia patients in each group. Parity was grouped into the following categories: 1, 2, ≥3. Education levels were categorized into 4 levels: elementary school or lower, junior high school, senior high school, college or above. The gestational age was selected to capture the effect of preterm (<37 weeks). The variable of family monthly income was categorized into 4 groups based on the distribution of family incomes in Taiwan's general population: <NT$15 000, NT$15 000–NT$30 000, NT$30 001–NT$50 000, ≥NT$50 001.

Statistical Analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the analyses in this study. Pearson χ2 tests were used to examine the differences between paternal schizophrenia and nonschizophrenia groups, in relation to characteristics of infant, mother, and father. Multivariate logistic regression analysis was also performed to explore the relationship between paternal schizophrenia and the risk of LBW, after adjusting for the characteristics of infant, mother, and father. A 2-sided P value of <.05 was considered statistically significant for this study.

Results

Of the total sample of 220,465 singleton live births, 175 (0.08%) infants had fathers diagnosed with schizophrenia. Details of the distribution of the characteristics of infant, father, and mother in relation to paternal schizophrenia and nonschizophrenia groups are provided in table 1. It shows that there was a significant relationship between LBW and paternal schizophrenia (P = .026); infants whose fathers had schizophrenia were more likely to have LBW than those whose fathers did not (12.6% vs 8.0%). Pearson χ2 tests also reveal that there were significant differences between the paternal schizophrenia and nonschizophrenia groups in terms of paternal age (P < .001) and paternal highest educational level (P < .001).

Table 2 describes the distribution of LBW by characteristics of infant, mother, and father. Pearson χ2 tests show that LBW was significantly related to the infant's gender, parity, paternal age and highest educational level, mother's marital status, gestational age, and whether a gestation was complicated with hypertension, and family monthly income (all P < .001).

The crude odds ratios of LBW for the paternal schizophrenia and nonschizophrenia groups are presented in table 3. For infants whose fathers had schizophrenia, the unadjusted odds of LBW was 1.66 times (95% confidence interval [CI] = 1.06–2.60, P < .05) that of their counterparts whose fathers had no schizophrenia. Rather interestingly, the unadjusted odds of LBW consistently decreased as paternal highest educational level increased. The unadjusted odds of LBW also decreased with increasing family monthly incomes.

Details of the adjusted odds ratios for the risk of LBW by paternal schizophrenia are also provided in table 3. As the table shows, following adjustment for the infant's age, parity, paternal age and highest educational level, gestational age, mothers' marital status, and family monthly income, infants whose father had schizophrenia were found to be 1.58 (95% CI = 1.10–2.52, P < .05) times more likely to have LBW than their counterparts whose fathers had no schizophrenia.

Discussion

To the best of our knowledge, this is the first nationwide population-based study to explore the association between LBW and paternal schizophrenia. Our study demonstrated that paternal schizophrenia is significantly associated with LBW; the offspring of fathers with schizophrenia were 1.58 times more likely to be born underweight than those whose fathers had no schizophrenia, after adjusting for other characteristics of infant, mother, and father. This finding is consistent with prior studies that reported associations between paternal characteristics and variations in birthweight.5–8

However, our finding would seem to contradict results of a study by Webb et al12 that failed to observe a significant relationship between paternal schizophrenia and fatal birth defects in Denmark. Besides different outcome measures, one possible reason for this difference is that a substantial part of infants suffering fatal birth defects (15%) lacked registered fatherhood data. Indeed, one study by Tan et al18 demonstrated that missing paternal information was associated with the risk of adverse birth outcomes. One study by Basso and Wilcox19 indicated that missing paternal vital statistics was more common for unmarried than married women. In contrast to the data used in study of Webb et al.,12 due to the mandatory registration of all birth information and a very low rate (about 3% in 2001) of single motherhood in Taiwan, only 0.3% of infants in our sample were missing fatherhood data. For these reasons, the comprehensive dataset in Taiwan provides a unique opportunity to clarify the association between paternal schizophrenia and LBW.

The mechanisms underlying the increased risk of LBW among infants of fathers with schizophrenia remain unclear.
The studies by Kramer\textsuperscript{20} and Bennedsen\textsuperscript{11} have categorized potential LBW determinants as follows: genetic and constitutional factors, obstetric factors, toxic exposures, smoking, alcohol, psychological factors, socioeconomic factors, maternal morbidity during pregnancy, and antenatal care. In our study, the association between paternal schizophrenia and LBW risk remained, even after adjusting for possible confounding socioeconomic factors and maternal morbidity during pregnancy. Furthermore, the NHI provides free antenatal care for all pregnant women in Taiwan. Hence, lack of access to antenatal care is unlikely as a major contributory factor to LBW among infants with fathers with schizophrenia in Taiwan.

Prior studies have demonstrated that schizophrenia has a strong tendency to be transmitted genetically to offspring.\textsuperscript{21,22} If LBW is a result of genetic liability instead of an environmental teratogen, it could lend support to the neurodevelopmental hypothesis of schizophrenia. That is, poor fetal growth related with genetic inheritance from a father with schizophrenia results in LBW, and LBW is, in turn, associated with developing schizophrenia in the future, as indicated by many studies.\textsuperscript{23} Thus, it may be worth following up on LBW offspring to see if they may be susceptible to increased risk of schizophrenia.

Besides genetic effects directly resulting from paternal schizophrenia, the use of psychotropic medications and particular health risk behaviors among fathers with schizophrenia could impact fetal growth in various ways. Furthermore, partners of fathers with schizophrenia may experience more stress during their pregnancies compared with mothers without partners with schizophrenia. Stress during pregnancy is associated with LBW.\textsuperscript{24}

This present study also found that the odds of LBW consistently decreased with the increasing paternal

Table 1. Comparisons of Paternal Schizophrenia and Nonschizophrenia Groups in Relation to Sociodemographic Characteristics and Gestational Comorbid Medical Disorders in Taiwan, 2001 (n = 220,465)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Paternal Schizophrenia Patients</th>
<th>Paternal NonSchizophrenia Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>22</td>
<td>17,617</td>
<td>8.0</td>
</tr>
<tr>
<td>≥2500</td>
<td>153</td>
<td>202,673</td>
<td>92.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>93</td>
<td>114,546</td>
<td>52.0</td>
</tr>
<tr>
<td>Female</td>
<td>82</td>
<td>105,744</td>
<td>48.0</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>104,283</td>
<td>47.3</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>80,922</td>
<td>36.7</td>
</tr>
<tr>
<td>≥3</td>
<td>31</td>
<td>35,085</td>
<td>15.9</td>
</tr>
<tr>
<td>Paternal characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;30</td>
<td>61</td>
<td>87,422</td>
<td>39.7</td>
</tr>
<tr>
<td>30–34</td>
<td>47</td>
<td>80,910</td>
<td>36.7</td>
</tr>
<tr>
<td>&gt;34</td>
<td>67</td>
<td>51,958</td>
<td>23.6</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Elementary school or lower</td>
<td>4</td>
<td>4235</td>
<td>1.9</td>
</tr>
<tr>
<td>Junior high school</td>
<td>51</td>
<td>46,571</td>
<td>21.1</td>
</tr>
<tr>
<td>Senior high school</td>
<td>113</td>
<td>135,276</td>
<td>61.4</td>
</tr>
<tr>
<td>College or above</td>
<td>7</td>
<td>34,208</td>
<td>15.5</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>.308</td>
</tr>
<tr>
<td>Married</td>
<td>166</td>
<td>213,683</td>
<td>97.0</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>6607</td>
<td>3.0</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td></td>
<td></td>
<td>.952</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1186</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>174</td>
<td>219,104</td>
<td>99.5</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>326</td>
<td>0.2</td>
</tr>
<tr>
<td>No</td>
<td>175</td>
<td>219,964</td>
<td>99.8</td>
</tr>
<tr>
<td>Family monthly income (in NT$)</td>
<td></td>
<td></td>
<td>.062</td>
</tr>
<tr>
<td>&lt;15 000</td>
<td>70</td>
<td>67,561</td>
<td>30.7</td>
</tr>
<tr>
<td>15 000–30 000</td>
<td>43</td>
<td>59,422</td>
<td>27.0</td>
</tr>
<tr>
<td>30 001–50 000</td>
<td>41</td>
<td>60,568</td>
<td>27.5</td>
</tr>
<tr>
<td>&gt;50 000</td>
<td>21</td>
<td>32,739</td>
<td>14.9</td>
</tr>
</tbody>
</table>
This finding is consistent with observations by Parker and Schoendorf in the United States. They used 1984–1988 data from the National Center for Health Statistics and found that the odds of low and very LBW decreased with increasing parental education. They furthermore concluded that parental education had independent effects on LBW. Unlike prior studies in regions or nations where there are diverse races, over 98% of Taiwan residents are of Han Chinese ethnicity, so the composition of the population is relatively homogenous. Therefore, our study can avoid possible confounding effects of race.

In addition to the abovementioned advantages, this study has other strengths. Because it used nationwide population-based datasets linking the NHIRD with birth and death certificates, its robust findings can be generalized to the population as a whole. Second, the large sample size provides ample statistical power to detect differences between the paternal schizophrenia and non-paternal schizophrenia groups, after adjusting for confounding variables.

The findings of this study need to be interpreted within the context of 4 limitations. First of all, although we have adjusted for the influence of some potential paternal, maternal, and pregnancy-specific confounders, information such as mothers’ or fathers’ smoking history, substance abuse, alcohol consumption, nutrition, and body mass index (particularly prepregnancy maternal body mass index) are not available through our datasets. These factors increase the risk of adverse pregnancy outcomes. However, our study excludes all mothers with serious mental disorders in the registry of catastrophic illness, which may help isolate paternal from maternal genetic contribution. Secondly, because we identify fathers diagnosed with schizophrenia by the ICD-9-CM code from the registry of catastrophic illness released by the Bureau of the

### Table 2. Distributions of Low Birthweight (<2500 g) by Characteristics of Infant, Mother, and Father in Taiwan, 2001

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Birthweight</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>%</td>
</tr>
<tr>
<td>Infant characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8173</td>
<td>46.3</td>
</tr>
<tr>
<td>Female</td>
<td>9466</td>
<td>53.7</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9196</td>
<td>52.1</td>
</tr>
<tr>
<td>2</td>
<td>5816</td>
<td>33.0</td>
</tr>
<tr>
<td>≥3</td>
<td>2627</td>
<td>14.9</td>
</tr>
<tr>
<td>Paternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>7403</td>
<td>42.0</td>
</tr>
<tr>
<td>30–34</td>
<td>6082</td>
<td>34.5</td>
</tr>
<tr>
<td>&gt;34</td>
<td>4154</td>
<td>23.6</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school or lower</td>
<td>431</td>
<td>2.4</td>
</tr>
<tr>
<td>Junior high school</td>
<td>4327</td>
<td>24.5</td>
</tr>
<tr>
<td>Senior high school</td>
<td>10 552</td>
<td>59.8</td>
</tr>
<tr>
<td>College or above</td>
<td>2329</td>
<td>13.2</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
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<tr>
<td>Married</td>
<td>16 530</td>
<td>93.7</td>
</tr>
<tr>
<td>Others</td>
<td>1109</td>
<td>6.3</td>
</tr>
<tr>
<td>Gestational hypertension</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>243</td>
<td>1.4</td>
</tr>
<tr>
<td>No</td>
<td>17 396</td>
<td>98.6</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32</td>
<td>0.2</td>
</tr>
<tr>
<td>No</td>
<td>17 607</td>
<td>99.8</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 wk</td>
<td>9005</td>
<td>51.1</td>
</tr>
<tr>
<td>Others</td>
<td>8634</td>
<td>49.0</td>
</tr>
<tr>
<td>Family monthly income (in NT$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 000</td>
<td>6014</td>
<td>34.1</td>
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<tr>
<td>15 000–30 000</td>
<td>4775</td>
<td>27.1</td>
</tr>
<tr>
<td>30 001–50 000</td>
<td>4559</td>
<td>25.9</td>
</tr>
<tr>
<td>&gt;50 000</td>
<td>2291</td>
<td>13.0</td>
</tr>
</tbody>
</table>
NHI, the sample may not truly represent the population with schizophrenia. In addition, this dataset did not allow us to account for differences in schizophrenia severity among patients. Thirdly, because maternal psychiatric morbidity was obtained from the catastrophic illness registry, this study could not identify mothers with other nonlisted mental disorders that might also be related to fetal growth. Lastly, as the NHIRD data cannot include schizophrenia patients who never receive treatment, some potential sampling bias may remain.

Despite these limitations, this study has demonstrated that after adjusting for possible confounding factors relating to infants, mothers, and fathers, the offspring whose fathers had a diagnosis of schizophrenia had increased risk of LBW compared with those whose fathers had no schizophrenia. Our pioneering findings may pave the way for further studies on the possible genetic mechanisms linking parental schizophrenia and fetal development. It also suggests a need for more active monitoring and early intervention to counter potential LBW for pregnant women with husbands with schizophrenia.

Acknowledgments

Conflict of interest: No conflict of interest to declare.

References


