Pregnancy, delivery and neonatal outcomes among women living with Down syndrome. A matched cohort study, taken from a population database.

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Abstract

Objectives: Women with Down syndrome (DS) suffer from several health issues, however, their fecundity is not affected. Despite that, there are no studies in the literature to address pregnancy, delivery, or neonatal outcomes among women with DS. Design: We conducted a retrospective study using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample Database over 11 years from 2004 to 2014. Methods: A delivery cohort was created using ICD-9 codes. ICD-9 code 758.0 was used to extract the cases of maternal DS. Pregnant women with DS (study group) were matched based on age and health insurance type to women without DS (control) at a ratio of 1:4. A multivariant logistic regression model was used to adjust for statistically significant variables (P-value < 0.5). Results: There were a total of 9,096,788 deliveries during the study period. Of those, 185 pregnant women were found to have DS. The matched control group was 740. Maternal pregnancy risks mostly did not differ between those with and without DS including pregnancy-induced PIH, gestational diabetes, preeclampsia, PPROM, chorioamnionitis, cesarean section, operative vaginal delivery, or blood transfusion (P >0.05, all). However, they were at extremely increased risk of delivering prematurely (aOR 3.86, 95% CI 1.25-11.93), and to have adverse neonatal outcomes such as small for gestational age (aOR 13.13, 95% CI 2.20-78.41), intrauterine fetal demise (aOR 20.97, 95% CI 1.86-237.02), and congenital anomalies (aOR 9.59, 95% CI 1.47-62.72). Conclusion: Women with DS should be counseled about their increased risk of premature delivery and adverse neonatal outcomes.

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Abstract

Objectives: Women with Down syndrome (DS) suffer from several health issues, however, their fecundity is not affected. Despite that, there are no studies in the literature to address pregnancy, delivery, or neonatal outcomes among women with DS.

Design: We conducted a retrospective study using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample Database over 11 years from 2004 to 2014.

Methods: A delivery cohort was created using ICD-9 codes. ICD-9 code 758.0 was used to extract the cases of maternal DS. Pregnant women with DS (study group) were matched based on age and health insurance type to women without DS (control) at a ratio of 1:4. A multivariant logistic regression model was used to adjust for statistically significant variables (P-value < 0.5). **Results:** There were a total of 9,096,788 deliveries during the study period. Of those, 185 pregnant women were found to have DS. The matched control group was 740. Maternal pregnancy risks mostly did not differ between those with and without DS including pregnancy-induced PIH, gestational diabetes, preeclampsia, PPROM, chorioamnionitis, cesarean section, operative vaginal delivery, or blood transfusion (P $>$0.05, all). However, they were at extremely increased risk of delivering prematurely (aOR 3.86, 95% CI 1.25-11.93), and to have adverse neonatal outcomes such as small for gestational age (aOR 13.13, 95% CI 2.20-78.41), intrauterine fetal demise (aOR 20.97, 95% CI 1.86-237.02), and congenital anomalies (aOR 9.59, 95% CI 1.47-62.72).

Conclusion: Women with DS should be counseled about their increased risk of premature delivery and adverse neonatal outcomes.

Key words:

Down syndrome; maternal pregnancy risks; neonatal outcome; premature delivery; small for gestational age; congenital anomalies.

Introduction:

Down syndrome (DS), is the most common non-sex chromosome duplication disorder in living humans, with a prevalence of 1 in 800 births worldwide [1,2]. In 95% of the cases, DS is caused by the existence of an extra copy of chromosome 21 resulting in trisomy[3]. Less frequently, translocation and mosaicism can lead to DS [2,3].

Individuals with DS have typical physical characteristics including short stature, up slanted palpebral fissures, flat nasal bridge, microcephaly, nuchal folds. hypotonia, and broad, short hands[1,3]. DS is associated with many medical conditions including musculoskeletal disorders, congenital heart defects, seen in up to 50% of those affected, gastrointestinal malformations such as Hirschsprung's disease, respiratory disease, hematologic malignancies, as well as hearing and visual problems [1,3,4]. Autoimmune diseases including Hashimoto's disease, celiac disease and Type I diabetes mellitus are common in patients with DS[1]. Individuals with DS often suffer from obesity that occurs in 25% of children and 50% of adults [1]. Down syndrome leads to a spectrum of intellectual disability and neurodevelopmental problems including limited social awareness, decreased motor coordination, and an increased incidence of autism spectrum disorder [1]. However, five percent of people with DS have an IQ close to normal threshold [5].

People with Down syndrome rarely reproduce, although the information on exact statistics is limited. Women with DS are fertile and a number of cases of pregnancy in DS mothers have been previously reported[6–8]. However, the literature suggests that women with DS are more likely to have early menopause and a decrease in the levels of anti-Mullerian hormone. It is thought that early menopause is secondary to reduced ovarian reserve [5].

To our knowledge, there are no studies in the literature to address pregnancy, delivery, or neonatal outcomes among women living with DS. Hence, we utilized a population database to address the paucity of data around pregnancy outcomes in women with DS.

Materials and Methods

We conducted a retrospective population-based cohort study utilizing data from the Health Care Cost and Utilization Project-Nationwide Inpatient Sample database (HCUP-NIS) over a period of 11 years, from 2004 to 2014. The HCUP-NIS is the largest inpatient sample database in the United States and is comprised of hospital inpatient stays submitted by hospitals throughout the entire country. Each year, the database provides information relating to 7 million inpatient stays, including patient characteristics, diagnosis, and procedures. The data represent more than 97% of inpatient discharges from community hospitals. A cohort of deliveries between 2004 and 2014 inclusively was created, using international classification of diseases, ninth edition, Clinical Modification (ICD-9-CM) diagnostic codes: 634x-679x, V22x, V23x, or V27x, and ICD-9-CM procedural codes: 72x -75x. Furthermore, the cohort was limited to admissions that resulted in a delivery or a maternal death using ICD-9-CM codes: 650x, 677x, or 651x-676x, and ICD-9-CM procedure codes: 72x, 73x, 74.0, 74.1, 74.2, 74.4 or 74.99, so that each subject was included once per pregnancy. Women with DS were identified using ICD-9 code 758.0, all women negative for DS comprised the control group. ICD-9 codes were also used to identify demographic characteristics, as well as pregnancy, delivery, and neonatal outcomes. Baseline clinical characteristics included age, race, income, insurance type, hospital type, previous Cesarean section (C/S), multiple gestations, tobacco use, obesity defined as body mass index (BMI) [?]30 kg/m2, as well as pre-gestational hypertension (HTN), diabetes, and thyroid disease. Pregnancy outcomes included gestational diabetes, Placenta previa, and pregnancy-induced hypertension as a group of gestational hypertension, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on underlying hypertension. Delivery outcomes included preterm delivery, preterm premature rupture of membrane (PPROM), abruption placenta, chorioamnionitis, mode of delivery, wound complication, maternal infection, hysterectomy, blood transfusion, venous thromboembolism (VTE), and maternal death. Maternal infections were composed of chorioamnionitis, septicemia during labor, postpartum endometritis, septic pelvic, or peritonitis. Wound complications were defined as infection, hematoma, hemorrhage or disruption of C/S or perineal wound. VTE included deep vein thrombosis (DVT) and pulmonary embolism during pregnancy, intrapartum or in the postpartum period. The neonatal outcomes included small for gestational age (SGA), congenital anomalies, and intrauterine fetal demise (IUFD). An initial analysis was performed to identify the prevalence of pregnant women with DS per year over the entire duration of the study. We compared the demographic and clinical characteristics of women with DS to those without DS by using Chi-square tests. Pregnant women with DS (study group) were matched based on age and health insurance type to women without DS (control) at a ratio of 1:4. Subsequently, multivariate stepwise logistic regression analyses were conducted to explore associations between DS and maternal and neonatal obstetrical outcomes through the calculation of odds ratios (OR) and 95% confidence intervals (CI). The regression models were adjusted for the potential confounding effects of maternal baseline clinical characteristics that were statistically different (p [?] 0.05) per group. All analyses were performed using SPSS 23.0 (IBM Corporation, Chicago, USA) software. This study used exclusively publicly accessible, anonymized data; hence, according to articles 2.2 and 2.4 of Tri-Council Policy statement (2010), institutional review board approval was not required.

Results

There was a total of 9,096,788 deliveries documented between 2004 and 2015, inclusive. Out of those, 185 women had a documented diagnosis of Down syndrome. The prevalence of women with DS varied from 1.48 to 3.14 per 100,000 women during the study period (p-value <.001) (Figure 1).

The baseline maternal demographic and clinical characteristics of our study population are summarized in Table 1. Pregnant women with Down Syndrome, compared with the control group, were more likely to be black and to smoke or use drugs during the pregnancy (15.4% vs. 5.8%, 7.6% vs. 3.5% and 4.3% vs. 1.2% respectively). There were no significant differences between the two groups concerning age, income, or insurance plan. Patients with Down syndrome did not have a higher prevalence of pre-existing metabolic conditions including obesity, chronic hypertension, pregestational diabetes or thyroids disease and were not more likely to have a multiple gestation compared to the control group.

The association between DS in women and adverse pregnancy and delivery outcomes, while controlling for confounding variables, are outlined in Table 2. Women with Down syndrome did not have an increased risk of developing pregnancy induced hypertension, gestational hypertension, preeclampsia and gestational diabetes mellitus, compared to the control group. Down syndrome was not associated with adverse delivery outcomes including PPROM, chorioamnionitis, operative vaginal delivery, cesarean delivery, spontaneous vaginal delivery, postpartum hemorrhage, length of stay and transfusion. Women with Down syndrome were more likely to have a preterm delivery (aOR 3.86, 95% CI 1.25-11.93).

The association between pregnant women with DS and neonatal outcomes, while controlling for confounding variables, are outlined in Table 3. Our results demonstrate staggeringly increased risks of intrauterine fetal demise (aOR 20.97, 95% CI 1.86-237.02). Neonates born to women with Down syndrome are overwhelmingly more likely to be small for gestational age (aOR 13.13, 95% CI 2.20-78.41) and to have congenital anomalies (aOR 9.59, 95% CI 1.47-62.72).

Discussion

The study's objective was to evaluate the pregnancy, delivery and neonatal outcomes in mothers diagnosed with DS.

The medical literature has demonstrated that individuals with DS have higher rates of thyroid dysfunction including congenital hypothyroidism, thyroid autoimmunity such as Hashimoto's disease or Grave's disease[9–11]. In addition, individuals with DS have a 3 to 4 fold increased risk of developing type 1 diabetes mellitus, which occurs at a younger age compared to individuals without DS[10–12]. Furthermore, DS increased the risk of developing obesity in children and adults [10]. Surprisingly, there was no increased prevalence of thyroid disease, pregestational diabetes or obesity in mothers with DS in our cohort. It is possible, that our sample size of mothers with DS was too small to detect the increased risk of these endocrinologic disorders. Another theory is that women with DS and thyroid disease, diabetes or obesity were less likely to conceive and deliver a baby than women with DS without these medical conditions.

Women with DS maintain some level of fertility, since many case reports have described pregnancies to mothers with DS [6–8,17]. It is possible that women with DS suffer from subfertility because they have a relatively low risk of fecundity based on the number of case reports in the literature. However, again bias exists with possible family pressure to practice safe birth control applied by family members particularly if the subjected with DS could not care for a child. Subfertility in women with DS, if it exists is hypothesized to be secondary to premature ovarian dysfunction [5,18].

It has been suggested in the literature that one in three to one in two infants born to mothers with DS, have DS themselves[5,7,20]. Women with trisomy 21 would be expected to produce an equal number of gametes 23 X and gametes 24 X + 21[6]. This should lead to an equal number of infants with DS and with a normal karyotype. However, some evidence in the literature has suggested that the frequency of DS infants born to mothers with DS could be lower. It is possible that this variation is due to the selective advantage of euploid gametes [6].

Women with DS in our cohort had a statistically significant increased risk of having a preterm delivery (p=0.02). Literature suggests that mothers with DS are at increased risk of preterm delivery[6]. The increased prevalence of PTD could be partially explained by the risk contributed by carrying an infant with DS, as mothers carrying DS infants are known to be at increased risk of PTD[21,22]. Furthermore, another

contributing factor to PTD could the increased risk of comorbidities in mothers with DS.

Our results demonstrated that infants born to mothers with DS, are almost 1000% more likely to have congenital anomalies compared to the control group. This could likely be explained by increased prevalence of DS infants in mothers with DS as well as other abnormalities not related to DS in the offspring [5,20]. It has been well recognized in the literature that infants with DS are more likely to have congenital anomalies and approximately 60 to 64% of children with DS have at least one major anomaly, with the most common ones being cardiac anomalies, digestive system anomalies and respiratory system anomalies [22–24]. The literature also described that many offspring to women with DS were associated with other malformation and cognitive deficit and no DS [7,20]. However, this is a single study and the question remains, whether infants without DS, born to mothers with DS have an increased risk of congenital anomalies?

Furthermore, our study found that infants born to mothers with DS are 1300% more likely to be SGA compared to infants born to mothers without DS. This is likely partially due to the increased risk of having a DS infant in mothers with DS. Although limited, the available data suggests that infants born to mothers with DS have low birth weight[6,21,22]. However, it is possible that being born to a mother with DS confers an additional risk to being SGA. A study by Rani et al. summarized cases of DS reported in the literature and suggested that babies born to mothers with DS, at term, are at increased risk of having low birth weight, even if they had a normal karyotype[6].

Mothers with DS were almost 2100% more likely to have an IUFD compared to mothers without DS. There is an increased likelihood that mothers with DS carry a child with DS which in itself has been associated with an increased risk of IUFD [21–23]. A study by Morris and al. demonstrated that in mothers carrying DS fetuses, between the time of chorionic villus sampling and term an estimated 43 % of pregnancies ended in miscarriage or stillbirth, between the time of amniocentesis and birth [23]. Furthermore, we can hypothesize that maternal aneuploidy increases the risk of other aneuploidies in the fetus which can lead to an increased risk of IUFD. However, there is no evidence in the literature regarding the genetics of stillborn infants to mother with DS.

Although our study showed that children born to mothers with DS are at increased risk of malformation, it would be interesting to know the type of congenital malformations in the infants born to mothers with DS. Furthermore, It would also be interesting to know if rates of complications differed between mothers with complete and mosaic DS. This data is unavailable in the literature.

Strengths and limitations:

One of the weaknesses of this study is that the database does not permit the authors to determine the prevalence of DS diagnosis in infants born to mothers with DS. This could help us determine if children born to mothers with DS are at increased risk of other malformations, except DS. Another limitation of this study is the lack of clinical information such as congenital anomalies in the mothers and their intellectual disability which could have attributed to determining if mothers with less comorbidities and higher IQ are more likely to become mothers.

Despite the drawbacks of our study, it has several strengths. This database included 9 million women which permitted us to select a well matched control group. It is the first study to look into obstetric outcomes in mothers with DS with a sample size of 185 pregnancies in mothers with DS. The remaining published literature is mainly case-reports.

The study contained data from 2004 to 2014 inclusively and was based on ICD-9 codes. In 2015, ICD-10 codes were introduced into the database, and with which ICD-9 codes are not comparable. As such, we feared that a new code would jeopardize the existing validated codes in the literature. As such, data from 2015 onward which was available at the time of analysis was not included in this study.

Conclusions:

To our knowledge, this is the first study to look into the association between DS in mothers and obstetric

outcomes. In conclusion, our study showed that pregnant women with DS have higher risk to of having preterm delivery and IUFD. In addition, infants born to mothers with are more likely to be SGA and to have congenital anomalies. Women with DS should be counseled preconceptionally and prenatally about their increased risk of premature delivery and adverse neonatal outcomes. Intervention such as screening for and enrolling in drug or smoking cessation programs might be beneficial in eliminating some but not all of these adverse outcomes.

Disclosure of interests:

There are no financial, personal, political, intellectual or religious interests to declare

Contribution to authorship:

AA&HB&AB&MD designed the study. HB&AB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HB&AB acquired the data and performed statistical analysis. AA&MP wrote and drafted the manuscript. MD contributed to study design and to statistical analysis and interpretation of data. All authors provided critical revision of the manuscript.

Details of ethics approval:

This study used exclusively publicly available data; hence, according to the Tri-Council Policy statement (2010), institutional review board approval was not required

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