

Pregnancy, delivery, and neonatal outcomes among women with beta-thalassemia major: A population-based study of a large US database

Juliette St-Georges

Université de Montréal: Universite de Montreal <https://orcid.org/0009-0003-3672-3593>

Abdullah Alnoman

King Abdulaziz University

Ahmad Badeghiesh

King Abdulaziz University

Haitham Baghlaf

baghlafh@gmail.com

University of Tabuk

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Abstract

Purpose:

We explored the effect of beta-thalassemia major on pregnancy and delivery outcomes in non-endemic area, utilizing USA population database.

Methods:

This is a retrospective study utilizing data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample. A cohort of all deliveries between 2011 and 2014 was created using ICD-9 codes. Patients with beta-thalassemia major were identified and matched to patients without beta-thalassemia based on age, race, income quartile and type of health insurance at a ratio of 1:20. Baseline characteristics were compared between the groups using Chi-square and Fischer's exact tests, as appropriate. Univariate and multivariate analyses were conducted for pregnancy, delivery and neonatal outcomes to estimate the unadjusted and adjusted odds ratio, respectively.

Results:

Out of 3,070,656 pregnancies over the study period, beta-thalassemia major complicated 445 pregnancies. Patients with beta-thalassemia were more likely to have thyroid disorders and previous C-section (p -value < 0.05). There were no differences in pregnancy outcomes such as gestational hypertension, preeclampsia, gestational diabetes, and placenta previa. C-section was 30% more likely to be the method of birth (aOR 1.30, 95%CI 1.03–1.63) and there was more than three-fold increased in rate of blood transfusion (aOR 4.69, 95% CI 3.02–7.28) among participants with beta-thalassemia major. Mothers with Beta-thalassemia, almost, were 70% more likely to have a neonate small for gestational age (aOR 1.68, 95%CI 1.07–2.62).

Conclusions:

Women with beta-thalassemia major are more likely to give birth by C-section, require blood transfusion and have small for gestational age neonates. Counseling patients with beta-thalassemia about these risks and increased antenatal surveillance is advised.

What does this study add to the clinical work

Due to continuous immigration throughout the world, certain diseases that were endemic at certain geographical areas are now encountered in other parts of the world. This study contributes to our understanding of pregnancy outcomes among women living with beta-thalassemia major who deliver in the United States. The findings will better inform counselling efforts regarding potential complications

for these patients.

Introduction

Beta-thalassemia are recessively inherited disorders of hemoglobin synthesis [1]. Beta-thalassemia affects approximately 1.5% of the world population, and an estimated 40,000 newborns are diagnosed with the condition annually [1]. Pregnant women and newborns affected by beta-thalassemia are at increased risk of complications due to underlying physiological and hemodynamic changes [2]. Possible complications associated with beta-thalassemia include but not limited to cardiac, endocrine, fetal cephalopelvic disproportion, increased incidence of cesarean section (C-section) [3] and infants being small for gestational age (SGA) [4].

Several studies on pregnancy in beta-thalassemia patients were published, reporting various rates of complications including transfusion, but lacked comparison with control groups and cohorts seldom included more than 100 participants [5–8]. More recent retrospective cohort studies validated the outcomes described in the case series, but were set in France, Israel, Thailand and Japan, populations with traditionally higher prevalence of beta-thalassemia than North America [9–13]. Therefore, the objective of this study was to estimate the prevalence of beta-thalassemia major among pregnant patients, and to assess the adverse outcomes in pregnancies complicated with beta-thalassemia major using a population database from the United States of America.

Materials and Methods

We conducted a retrospective population-based study utilizing data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample database (HCUP-NIS) over four years. The HCUP-NIS is publicly available, it comprises hospital inpatient stays submitted by hospitals in 48 states and the District of Columbia. Seven million inpatient stays are provided yearly, including patient characteristics, diagnosis, and procedures. The data are representative of around 20% of admissions to United States hospitals, covering 96% of the American population geographically.

We evaluated deliveries between 2011 and 2014 inclusively, using the international classification of diseases, ninth edition, clinical modification (ICD-9-CM). Diagnostic codes for delivery related discharge diagnoses including maternal death were extracted: (650.xx, 677.xx, 651.xx–676.xx where the fifth digit is 0, 1 or 2). Birth-related procedures were also extracted: (72.x, 73.x, 74.0–74.2, 74.4, 74.99). Missing data was evaluated and found to be randomly distributed. Therefore, Markov Chain Monte Carlo (MCMC) model was used to impute the data. After that, hemoglobinopathies other than beta-thalassemia major were excluded using the appropriate codes. Patients with beta-thalassemia major were identified using ICD-9-CM diagnostic code 282.44 and they comprised the exposed group, while the others represent the control group. The cases of beta-thalassemia major were then matched to the control group based on age, race, income quartile, and insurance type in a ratio of 1:20.

Demographic characteristics as well as pregnancy, delivery and neonatal outcomes were identified using ICD-9-CM diagnostic and procedural codes. Baseline maternal characteristics included age, race, income, insurance type, obesity defined as body mass index (BMI) of $\geq 30\text{kg/m}^2$, previous C-section, smoking status during pregnancy, chronic hypertension, pregestational diabetes mellitus, pre-existing thyroid disease, multiple gestation, and in vitro fertilization (IVF). Pregnancy outcomes evaluated include gestational hypertension, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on pre-existing hypertension as individual and as a group under the umbrella of pregnancy induced hypertension. Also, gestational diabetes mellitus and placental previa were examined. Delivery outcomes evaluated include preterm premature rupture of membrane (PPROM), preterm birth, abruptio placenta, chorioamnionitis, operative vaginal delivery, C-section, spontaneous vaginal delivery, postpartum hemorrhage (PPH), wound complications, transfusion, maternal infection, and hysterectomy. Wound complications were defined as infection, hematoma, hemorrhage, or disruption of C-section or perineal wound. Maternal infections were defined as septicemia during labor, postpartum endometritis, septic pelvic, or peritonitis. Lastly, neonatal outcomes evaluated include SGA defined as birth weight less than the tenth percentile, intrauterine fetal demise (IUFD), and congenital anomalies.

First, the overall prevalence of beta-thalassemia major was estimated, then annual prevalence over the study period was calculated. Second, maternal characteristics were compared between women with and without beta-thalassemia major using the chi-square and Fisher's exact tests as appropriate. The maternal characteristics of patients with beta-thalassemia major were also compared to all the deliveries identified within the database, prior to matching and exclusion of other hemoglobinopathies, to ensure the control group is representative of the cohort. Third, unadjusted odds ratio (OR) and 95% confidence intervals were estimated by univariate logistic regression analysis to explore associations between beta-thalassemia major and pregnancy, delivery, and neonatal outcomes. Finally, multivariate logistic regression analysis was conducted to adjust for the potential confounding effects of maternal characteristics on pregnancy and delivery outcomes, and of pregnancy on delivery and neonatal outcomes. To protect participants, avoid re-identification, and comply with Health Insurance Portability and Accountability Act (HIPAA) all outcomes with less than 11 occurrences were presented as such. The SPSS 23.0 (IBM, Corporation, Chicago, USA) software was used for statistical analysis. This study used exclusively publicly accessible, anonymized data; hence, according to articles 2.2 and 2.4 of the Tri-Council Policy statement (2018), institutional review board approval was not required.

Results

There was a total of 3,070,656 deliveries documented between 2011 and 2014, inclusive. Out of those pregnancies, 445 had a diagnosis of beta-thalassemia major. The control group was composed of 8,900 pregnancies, representing a 1:20 match between the exposed and control group, respectively. The prevalence rate of beta-thalassemia major increased significantly over the study period from 2.5 per 100,000 births in 2011 to 20.0 per 100,000 births in 2014 ($p < 0.001$) (Fig. 1).

The baseline maternal demographic and clinical characteristics of our study population are summarized in Table 1. There were no significant differences between the two groups concerning pre-existing metabolic conditions such as obesity, chronic hypertension, and pregestational diabetes. Multiple gestation and IVF did not differ between the groups. Women with beta-thalassemia major were more likely to suffer from pregestational thyroid disease, 7.9% vs 4.4%, (p-value = 0.001) and had a higher rate of previous C-section, 21.6% vs 17.7%, (p-value = 0.04).

Table 1
Demographic & clinical characteristics of women who delivered between 2004 and 2014

Characteristics	Beta Thalassemia N = 445 (%)	Control N = 8900 (%)	P-value
Age (years)			1.00
< 25	115 (25.8)	2,300 (25.8)	
25–34	249 (56.0)	4,980 (56.0)	
≥ 35	81 (18.2)	1,620 (18.2)	
Race			1.00
White	171 (38.4)	3,420 (38.4)	
Black	107 (24.0)	2,140 (24.0)	
Hispanic	40 (9.0)	800 (9.0)	
Asian and Pacific	89 (20.0)	1,780 (20.0)	
Native American	4 (0.9)	80 (0.9)	
Other	34 (7.6)	680 (7.6)	
Income quartiles			1.00
Less than 39,000	97 (21.8)	1,940 (21.8)	
\$39,000–47,999	105 (23.6)	2,100 (23.6)	
\$48,000–62,999	110 (24.7)	2200 (24.7)	
\$63,000 or more	133 (29.9)	2660 (29.9)	
Plan type			1.00
Medicare	6 (1.3)	120 (1.3)	
Medicaid	165 (37.1)	3,300 (37.1)	
Private including HMO	257 (57.8)	5,140 (57.8)	
self-pay	5 (1.1)	100 (1.1)	
Other	12 (2.7)	240 (2.7)	
Obesity	28 (6.3)	572 (6.4)	0.91
Previous CS	96 (21.6)	1578 (17.7)	0.04
Smoking during pregnancy	15 (3.4)	410 (4.6)	0.22
CS: caesarean section; HTN; hypertension; DM: diabetes mellitus; IVF: in vitro fertilization.			

Characteristics	Beta Thalassemia N = 445 (%)	Control N = 8900 (%)	P-value
Chronic HTN	< 11	205 (2.3)	0.70
Pregestational DM	< 11	97 (1.1)	0.34
Thyroid disease	35 (7.9)	396 (4.4)	0.001
Multiple gestation	< 11	175 (2.0)	0.68
IVF	< 11	47 (0.5)	0.68
CS: caesarean section; HTN; hypertension; DM: diabetes mellitus; IVF: in vitro fertilization.			

The association between beta-thalassemia major and adverse pregnancy and delivery outcomes are outlined in Table 2. Participants with B-thalassemia major did not have an increased risk of pregnancy induced hypertension, gestational hypertension, preeclampsia, eclampsia, preeclampsia and eclampsia superimposed on pre-existing hypertension and placenta previa. No events of eclampsia were experienced in the cases. Moreover, there were no significant differences in the rates of PPRM, preterm birth, abruptio placenta, chorioamnionitis, operative vaginal delivery, PPH, wound complications, maternal infection, and hysterectomy. Women with beta-thalassemia major were 30% more likely to deliver by C-section (aOR 1.30, 95% CI 1.03–1.63) and 370% more likely to require an intrapartum blood transfusion (aOR 4.69, 95% CI 3.02–7.28).

Table 2
Effect on maternal and delivery outcomes

Outcomes	Beta Thalassemia N = 445 (%)	Control N = 8,900 (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	P- value
Pregnancy outcomes^a					
Pregnancy induced hypertension	31 (7.0)	708 (8.0)	0.87 (0.60–1.26)	0.86 (0.59–1.25)	0.43
Gestational hypertension	< 11	320 (3.6)	0.62 (0.33–1.16)	0.61 (0.32–1.16)	0.14
Preeclampsia	19 (4.3)	325 (3.7)	1.18 (0.73–1.89)	1.18 (0.74–1.90)	0.49
Preeclampsia and Eclampsia superimposed on pre-existing HTN	< 11	80 (0.9)	0.50 (0.12–2.03)	0.46 (0.11–1.87)	0.28
GDM	43 (9.7)	776 (8.6)	1.12 (0.81–1.55)	1.07 (0.77–1.48)	0.69
Placenta previa	< 11	63 (0.7)	1.59 (0.64–3.98)	1.62 (0.65–4.06)	1.62
Delivery outcomes^a					
PPROM	< 11	111 (1.2)	1.08 (0.47–2.48)	1.10 (0.48–2.53)	0.81
Preterm delivery	29 (6.5)	497 (5.6)	1.18 (0.80–1.74)	1.18 (0.80–1.73)	0.41
Abruptio placenta	< 11	99 (1.1)	1.42 (0.66–3.08)	1.44 (0.66–3.12)	0.36
Chorioamnionitis	< 11	195 (2.2)	1.03 (0.54–1.95)	1.07 (0.56–2.03)	0.85
PPROM: preterm premature rupture of membrane; CS: cesarean section; PPH: postpartum hemorrhage.					
^a Adjusted for previous C-section, thyroid disease and year of diagnosis					

Outcomes	Beta Thalassemia N = 445 (%)	Control N = 8,900 (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	P- value
Operative vaginal delivery	19 (4.3)	414 (4.7)	0.91 (0.57– 1.46)	0.95 (0.59– 1.52)	0.83
CS	176 (39.6)	2,906 (32.7)	1.35 (1.11– 1.64)	1.30 (1.03– 1.63)	0.03
Spontaneous vaginal Delivery	250 (56.2)	5,580 (62.7)	0.76 (0.63– 0.92)	0.80 (0.64– 0.99)	0.04
PPH	15 (3.4)	296 (3.3)	1.01 (0.60– 1.72)	1.03 (0.61– 1.75)	0.91
Wound complications	< 11	22 (0.2)	0.91 (0.12– 6.76)	0.86 (0.12– 6.44)	0.89
Transfusion	26 (5.9)	111 (1.3)	4.76 (3.07– 7.38)	4.69 (3.02– 7.28)	< 0.0001
Maternal infection	12 (2.7)	227 (2.6)	1.06 (0.59– 1.91)	1.10 (0.61– 1.98)	0.75
Hysterectomy	< 11	12 (0.1)	1.62 (0.21– 12.46)	1.55 (0.20- 12.01)	0.67
PPROM: preterm premature rupture of membrane; CS: cesarean section; PPH: postpartum hemorrhage.					
^a Adjusted for previous C-section, thyroid disease and year of diagnosis					

The association between beta-thalassemia major and neonatal outcomes are outlined in Table 3. There were no significant differences in the rates of IUFD and congenital anomalies between the groups. However, patients with beta-thalassemia major were 70% more likely to have an SGA neonate. (aOR 1.68, 95% CI 1.07–2.62).

Table 3
Effect on neonatal outcomes^a

Outcomes	Beta Thalassemia N = 445 (%)	Control N = 8,900 (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
SGA	22 (4.9)	274 (3.1)	1.64 (1.05–2.56)	1.68 (1.07–2.62)	0.02
IUFD	< 11	44 (0.5)	1.37 (0.42–4.42)	1.34 (0.42–4.35)	0.62
Congenital anomalies	< 11	54 (0.6)	1.11 (0.35–3.57)	1.04 (0.32–3.34)	0.95

SGA: small for gestational age; IUFD: intrauterine fetal demise.

^a Adjusted for previous C-section, thyroid disease and year of diagnosis

The maternal characteristics of beta-thalassemia major patients compared with the total cohort of 3,070,656 patients are outlined in Table S1. There were no significant differences between beta-thalassemia major patients and the control group regarding income quartiles, rates of obesity, smoking during pregnancy, chronic hypertension, pregestational diabetes, thyroid disease, multiple gestation and IVF. As with the matched control group, more beta-thalassemia major patients had a history of C-section ($p = 0.02$) and had pregestational thyroid disease ($p < 0.0001$). Patient with beta-thalassemia major were more likely to be older ($p < 0.0001$), and have a private insurance ($p = 0.009$). Lastly, within the beta-thalassemia major group, there were more African American, Asian and pacific and Native American patients ($p < 0.0001$).

Discussion

The present study involved 445 women diagnosed with beta-thalassemia major, who delivered over a four-year period in USA. The control groups was composed of 8,900 participants. We chose a 1:20 case to control ratio to sufficiently power our study and allow us to better adjust for confounding variables. In USA, beta-thalassemia major remains a rare disease, with 341 expected affected newborn per year in North, Central and South America combined [14]. During our study, the yearly prevalence increased significantly from less than 5 per 100,000 births in 2011 to 20 per 100,000 births in 2014. The ICD-9 code for beta-thalassemia major was introduced in the year 2011, the start of our study period, and has been used since in American databases to successfully identify beta-thalassemia major cases [15]. The increasing prevalence over the study period, at a glance, is most likely the result of the utilization of the code following its introduction as seen with a steep slope in Fig. 1. However, this theory was not supported when we re-calculated the p-value (< 0.0001) after excluding the first year (2011). Another plausible explanation is the addition of carriers through migration from endemic regions and more

recent movements of refugees into USA [1, 16]. Our study is the first of its magnitude in a region where beta-thalassemia major is not endemic. It demonstrates the association of beta-thalassemia major diagnosis and risks of adverse delivery and neonatal outcomes.

First, our cohort of women diagnosed with beta-thalassemia major had higher rates of pregestational thyroid disease. Beta-thalassemia major patients are susceptible to iron overload due to the combination of chronic hemolytic anemia and repeated transfusions [1]. Endocrine complications such as hypothyroidism are explained by the endocrine tissue' sensitivity to iron toxicity and have been also well reported in recent reviews [3, 5, 17, 18].

This study also, demonstrated that patients in our cohort had higher rates of prior C-section and an increased risk of undergoing C-section during the observed pregnancy when compared to the control group. This finding was held truth even after adjusting for previous C-section as a confounding variable. These findings can be partially attributed to the short stature and the bone deformity observed in beta-thalassemia patients, causing concerns of cephalopelvic disproportion [3, 17]. Short stature in patients with beta-thalassemia major can be explained by the disturbances in the parathyroid function and calcium metabolism as well as hypogonadism secondary to excessive iron deposition [3]. Moreover, chronic anemia leading to extramedullary hematopoiesis and bone marrow expansion can cause remodeling to the pelvic bones, therefore increase the risk of cephalopelvic disproportion [1]. The adjusted risk of delivery by C-section was 30% more likely for beta-thalassemia major patients compared to the control group, with a prevalence of 39.6%. Our findings are concordant with the literature. In a recent narrative review, the increased risk of delivery by C-section for beta-thalassemia patients is described qualitatively[17]. In a study in France including 37 women with beta-thalassemia major and intermedia, C-section was performed in 53.6% of pregnancies, which was significantly more often than in non-carriers ($p = 0.002$). [13]. In all smaller case series studying patients with beta thalassemia major and intermedia, the prevalence ranges from 24% to all deliveries being done by C-section [7, 8, 19–22].

Our cohort did not find an association between beta-thalassemia major and increased risks of adverse pregnancy outcomes, including gestational hypertension, preeclampsia and placenta previa among others. A recent review reports similar risks of preeclampsia compared to the background population [17]. In our cohort, rates of gestational diabetes tended to be higher among the beta-thalassemia major patients (9.7% VS 8.6%), though the difference was not statistically significant ($p > 0.05$). The pooled prevalence of gestational diabetes is estimated at 14% globally and 7.1% in North America and Caribbean [23]. Certain reviews describe a clear association related to iron toxicity, with a prevalence as high as 15% [18, 24]. An observational study in China reported a prevalence of gestational diabetes as high as 17.9% [6] Two case series on six and four beta-thalassemia major pregnancies respectively reported no incidence of gestational diabetes [5, 25]. The literature does not provide a clear consensus regarding the association between beta-thalassemia and gestational diabetes, and this might be explored further in future studies.

During normal pregnancy, there is a state of accelerated erythropoiesis, with expansion of the total red blood cell volume with concurrent expansion of plasma volume, leading to dilutional anemia [2]. In the presence of ineffective erythropoiesis, beta-thalassemia major mothers require more transfusions during pregnancy [2, 18]. In our cohort, among beta-thalassemia major pregnancies, 5.9% required transfusions during delivery compared to 1.3% in the control group ($p < 0.0001$). In a review of reproductive health issues in beta-thalassemia major patients, a qualitative report of increased transfusion regimen during pregnancy is described [18]. In a case series, all beta-thalassemia major women achieving pregnancy required transfusions, with increasing red blood cells consumption during pregnancy [7]. In most studies, all beta-thalassemia major cases are transfused during the pregnancy course. However, intrapartum blood transfusion were not studied before. Our study, although demonstrated a more than threefold increased risk of transfusion (aOR 4.69 95%CI 3.02–7.28), this rate was less than previously reported as not all participants were transfused. The difference in the rate of blood transfusion among patients with beta-thalassemia major in our study compared to the literature is most likely because we address only transfusions received during the admission for delivery. Despite knowing that these patients were at risk of anemia, they required blood transfusion intrapartum, suggesting their hemoglobin level was not optimized at the time of delivery. Therefore, this study highlights the recommendation to optimize hemoglobin levels before entering labour.

Women with beta-thalassemia were 70% more likely to give birth to a small for gestational age neonate. The presence of anemia of any etiology during the first trimester is a risk factor for neonates being born small for gestational age [4]. A confounding factor that has been described is that due to subfertility, more women benefit from assisted reproductive technology, and have higher rates of multiple gestations and preterm births. Sayani and colleagues found that among women with transfusion dependent thalassemia, the rates of growth restricted fetuses is similar to that of the general population when corrected for multiple gestations [17]. A study from Thailand included 597 pregnant women with beta-thalassemia traits, the prevalence of low birth weight ($< 2500\text{g}$) was higher, but not the rates of small for gestational age compared to the control group [10]. A study based in China including 228 beta-thalassemia carriers, with 84.48% of mothers suffering from anemia, 5.95% of infants had low birth weight [6]. As mentioned in the previous paragraph, we recorded an increased rate of intrapartum blood transfusion among women with beta-thalassemia. Therefore, we can hypothesize that some of the patients in our studies had poorly controlled anemia, which in return increased their risk of having SGA newborns.

There are several limitations to our study, including its retrospective nature, lacking information on hemoglobin and transferrin levels as well as frequency of blood transfusion throughout the pregnancy. Moreover, the code for beta-thalassemia was introduced at the beginning of our study and this might have affected the real number of cases and masked other effects of beta-thalassemia major on outcomes. However, our findings would have a higher specificity and stronger correlation if the aforementioned is true. Furthermore, given that the database does not list different medications taken, we cannot control for the effect of iron chelating therapy on outcomes. On the other hand, this study has several strength advantages such as assessing large number of pregnancies in a non-endemic area for

beta-thalassemia major. In addition, excluding other hemoglobinopathies prior to selecting the cases has led to mitigate any chance that these findings could be as a result of a concurrent hemoglobinopathy other than beta-thalassemia major.

Conclusion

Our large database study, along with previous studies, demonstrated the association between maternal beta-thalassemia and obstetrical complications such as increased risk of delivery by C-section and of receiving intrapartum blood transfusion. Neonates had an increased risk of being born SGA. Women with beta-thalassemia should be counseled preconceptionally and prenatally about their increased risk in antenatal and neonatal adverse outcomes. Furthermore, studies comparing patients with different hemoglobin levels throughout pregnancy is recommended to assess the risk of beta-thalassemia major on SGA in none-endemic area.

Declarations

Funding: No funding was received for conducting this study.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Author contributions: A. Alnoman and H. Baghlaf contributed to the study conception and design. Material preparation, data collection and analysis were performed by A. Alnoman, A. Badeghiesh and H. Baghlaf. The first draft of the manuscript was written by J. St-Georges and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials and Ethics approval: This study used exclusively publicly accessible, anonymized data; hence, according to articles 2.2 and 2.4 of the Tri-Council Policy statement (2010), institutional review board approval was not required.

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Figures

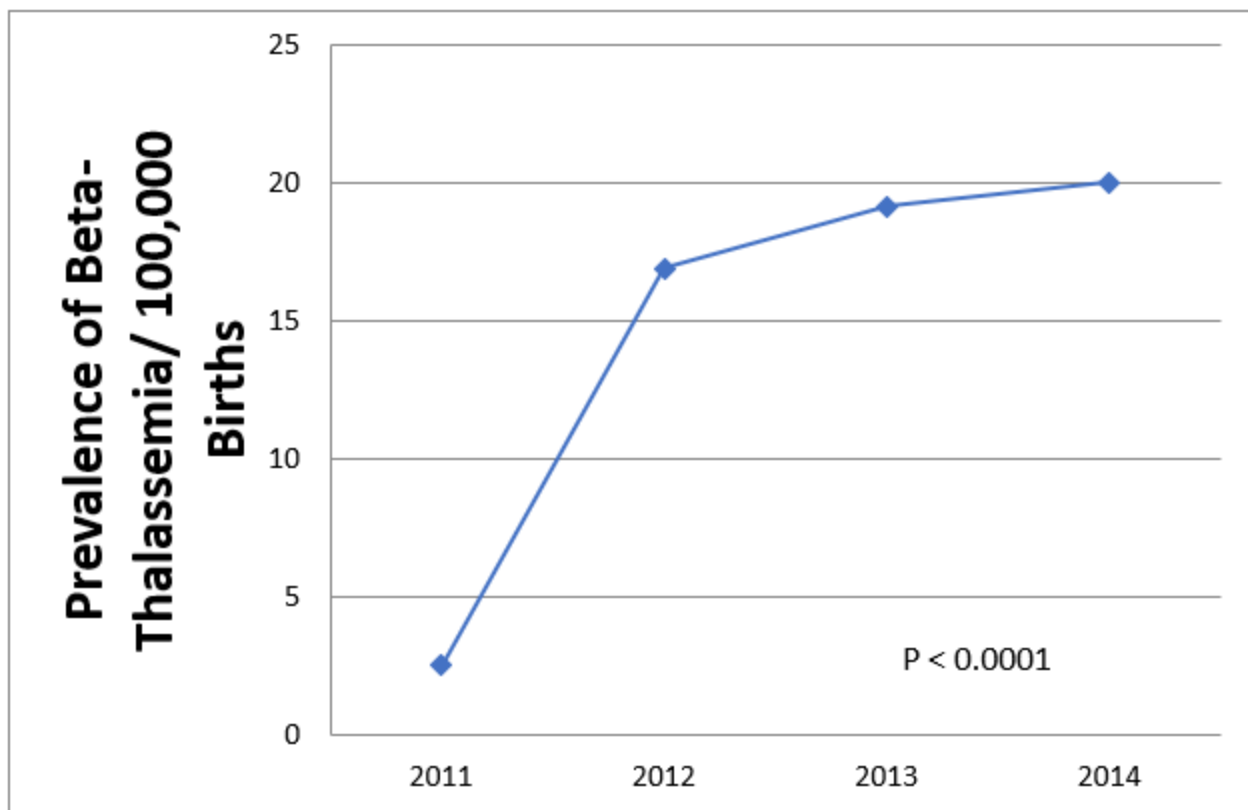


Figure 1

Annual prevalence of Beta-thalassemia among women who delivered between 2004 and 2014

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