Use of Prophylactic Iron Salts Supplementation During Gestation and Development of Gestational Diabetes Mellitus in Women From 2015 Pelotas (Brazil) Birth Cohort Study

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Abstract

Background

This study aims to evaluate the association between the use of iron salts during the first two trimesters in non-anemic women and the development of gestational diabetes mellitus (GDM).

Methods

The study used maternal data from 2015 Pelotas Birth Cohort. All non-anemic women at 24th week (N = 2463) were eligible for this study. GDM was self-reported by women. Crude and adjusted logistic regression were performed considering level of significance = 0.05.

Results

Among the women studied, 69.7% were exposed to prophylactic iron supplementation in the two first trimesters of gestation. The prevalence of GDM among those exposed was 8.7% (95%CI 7.4–10.1) and among those who were not exposed was 9.3% (CI95% 7.4–11.6). Iron supplementation was not associated with increased risk of GDM in crude (OR = 0.9; 95%CI 0,7–1,3) and adjusted analysis (OR = 1.1; 95% CI 0,8–1,6).

Conclusions

The results suggested that routine iron use in non-anemic pregnant women does not increase the risk of developing gestational diabetes. This evidence supports the existing national and international guidelines, whose recommendation is prophylactic iron supplementation for all pregnant women as soon as they initiate antenatal care in order to prevent iron deficiency anemia.

Background

Gestational Diabetes Mellitus (GDM) is a temporary condition, characterized by hyperglycemia, which occurs due to carbohydrate and glucose intolerance (1, 2). It begins for the first time during pregnancy and it usually, disappears shortly after delivery (1). Population estimates of hyperglycemia frequency in pregnancy are conflicting, because there are different criteria for GDM diagnosis, with prevalence varying from 1 to 18% of pregnant women in different populations and differences between guidelines (2, 3). In Latin America, for example, the 75 g 2-hour glucose test > 7.8 mmol / L or > 140 mg / dL is a diagnosis of GDM. In China,> 5.1 mmol / L or > 92 mg / dL sets GDM diagnosis(4).

GDM is responsible for many consequences in maternal-fetal health in the short and long term (3). The most common consequences among children are the increased risk of fetal macrosomia, neonatal hypoglycemia, shoulder dystocia, and hyperinsulinemia at birth. Mothers with GDM are at increased risk of preeclampsia, gestational hypertension, cesarean section, and polyhydramnios. In addition, there is an increased risk of fetal malformations, abortion, neonatal and perinatal mortality, as well as increased risk of maternal mortality (5–8). In the long term, the maternal effect of GDM is the elevated risk for the development of metabolic syndrome and type 2 diabetes(9). For the child, there is almost double the risk of developing childhood obesity and metabolic syndrome, compared to children born from non-diabetic mothers (9).

Another very prevalent problem during pregnancy is iron deficiency anemia, reaching 42.0% of all pregnant women (10). In this sense, current guidelines from World Health Organization (WHO) and Brazilian Ministry of Health recommend, in addition to adequate diet, prophylactic (routine) iron supplementation for all pregnant women, in order to satisfy the physiological needs of this mineral (11, 12). However, this universal prophylactic supplementation has been questioned, because according to some authors, high iron intake may increase the risk of GDM, especially for those women with normal hemoglobin levels in early pregnancy(13, 14), which has been reported as an independent risk factor for DMG (15).

Findings regarding the association between the use of iron salts and the development of gestational diabetes are new and still inconclusive, therefore, further studies are necessary to disentangle the possible relationship between the use of iron salts and GDM. In this study we aimed to evaluate the association between the use of iron salts in non-anemic women in early pregnancy and the development of GDM in a cohort of births whose mothers were followed up since the antenatal period.

Methods

This paper uses data from antenatal and perinatal studies from Pelotas' Birth Cohort of 2015 (C2015), which was conducted in the city of Pelotas in southern Brazil. The study invited all women living in the urban area of Pelotas who gave birth, including stillbirths, in the five maternity hospitals of the city, between January 1 and December 31, 2015.

Mothers were interviewed at the maternity hospital a few hours after delivery and answered a standardized questionnaire. They answered questions about antenatal period: demographic, socioeconomic, biological and behavioural issues, along with characteristics of pregnancy, delivery and medication use, including folic acid, iron salts and other vitamins and minerals. Furthermore, 75% of mothers who participated in the perinatal study were followed since the antenatal period by this cohort. More details of the study can be found in the cohort profile paper (16).

The analyses in this article were performed with all mothers from a perinatal follow-up who were eligible for this study (N = 2463) (Fig. 1). Anaemic pregnant women before 24th week (with record of at least one hemoglobin test < 11g / dL in the pregnant woman's antenatal card), were not included in the analyses.

For the outcome “gestational diabetes mellitus” self-reports were considered. The mothers answered the following question: “Did you have diabetes during pregnancy?”, followed by other question: “Did you have diabetes before pregnancy?”. Pregnant women who already had diabetes before becoming pregnant (n = 44) were excluded. Self-reported information about mother's knowledge of GDM, in the immediate postpartum, was validated through a study previously carried out in Pelotas' maternity, with high specificity (99.0%, 95%CI: 98.1; 99.6) and good sensitivity 73.0% (95%CI: 55.9; 86.2)(17).

The variables used in the analysis as possible confounding factors were: maternal age (collected in complete years and categorized as ≤ 19, 20–29, 30–46); ethnicity (self-reported by mothers as white, black or other); parity (total number of deliveries, including stillbirths and current pregnancy; later categorized as 1, 2, 3 or 4 or more); mother’s schooling (number of years of study, later categorized into four groups: 0–4, 5–8, 9–11 and 12 or more years) and family income expressed in local currency and converted into a multiple of minimum wage at the time of the perinatal interview (categorized as ≤ 1, 1.1 to 3.0, 3.1 to 6.0, 6.1 to 10 and > 10). A ‘minimum wage’ is a measure of the legal minimum monthly salary for formal employees in Brazil.

Family history of diabetes mellitus was reported by the mother at the 24-month follow-up, pre-pregnancy body mass index (BMI) was calculated by dividing pre-pregnancy weight by the square of maternal height, and categorised according to WHO criteria(18): underweight (< 18.5 kg/m^2); normal (18.5–24.9 kg/m^2); overweight (25.0–29.9 kg/m^2); and obese(≥ 30 kg/m^2) and smoking in pregnancy was considered “yes” when the mother reported smoking at least one cigarette a day, for at least 30 days.

Information regarding supplement use was taken from the following questions: *" Have you used or are you using any vitamin, calcium, folic acid or iron salts since you became pregnant*?”. If yes, the drug names were then questioned and for each drug reported a question about the trimester of use was asked: *“In which trimester of pregnancy did you use this medicine?” (*1st trimester / 2nd trimester, 3rd trimester).

From these questions, it was possible to generate the main exposure used in our analyses: “use of prophylactic iron in the first and / or second trimester of pregnancy”, which has been formulated using all iron compounds alone or in combination with other active substances, provided that iron was the main compound present. All analyses were performed in Stata *software* 15.0. Sample description was performed according to exposure and outcome (GDM) using the chi-square test. The association of iron supplements use with development of GDM was evaluated using logistic regression

The regression followed a previously established hierarchical conceptual model, which comprises three levels. The distal level included the sociodemographic variables and family history of diabetes; the second level included pre-gestational BMI, parity and smoke; and the proximal level included the use of iron salts. Variables with $p < 0.20$ were kept in the model to control confounding factors. For all statistical analyses, the significance threshold was set at $p < 0.05$.

The Federal University of Pelotas, School of Physical Education Ethics Committee, approved the study protocol (522.064). All mothers signed an informed consent form before being interviewed.

Results

Of the 2463 mothers who participated in this study, about half were between 20 and 29 years old (48.0%), most white skin colour (75.8%) and with more than nine years of schooling (72.1%). The predominant family income was 1.1 to 3 minimum wages (46.0%) and 47.0% of the mothers had pre-gestational BMI considered normal by WHO criteria (18). More than half of women were in their first pregnancy (52.7%), had no family history of gestational diabetes (55.5%) and most were non-smokers (86.6%) (Table 1).

Table 1
'Baseline characteristics of mothers participating in the perinatal cohort study (n = 4270) and eligible mothers (n = 2463). 2015 Pelotas (Brazil) Birth Cohort.

Variables	Perinatal sample		Eligible mothers	
	N (%)	**95% CI**	**N (%)**	**95% CI**
Age				
≤ 19	630 (14.8)	13.7–15.8	282 (11.5)	10.2–12.7
20–29	2021 (47.3)	45.8–48.8	1182 (48.0)	46.0–50.0
30–46	1618 (37.9)	36.4–39.4	998 (40.5)	38.5–42.4
Skin colour				
White	3005 (70.5)	69.1–71.8	1864 (75.8)	74.1–77.4
Black	680 (16.0)	14.8–17.1	305 (12.4)	11.1–13.7
Others	578 (13.5)	12.5–14.5	291 (11.8)	10.5–13.1
Schooling (years)				
≤ 4	394 (9.3)	8.3–10.1	168 (6.8)	5.8–7.8
5–8	1098 (25.7)	24.4–27.0	520 (21.1)	19.5–22.7
9–11	1463 (34.3)	32.8–35.7	894 (36.3)	34.4–38.2
≥ 12	1314 (30.7)	29.4–32.1	881 (35.8)	33.9–37.6
Family income (minimum wages)[a]				
≤ 1	512 (12.6)	11.6–13.6	222 (9.5)	8.3–10.6
1.1–3.0	1906 (47.0)	45.4–48.5	1077 (46.1)	44.0–48.0
3.1–6.0	1077 (26.5)	25.2–27.9	684 (29.2)	27.4–31.1
6.1–10.0	307 (7.5)	6.6–8.2	191 (8.2)	7.0–9.2
> 10.0	257 (6.4)	5.5–7.0	164 (7.0)	5.9–8.1
Pre-pregnancy body mass index (kg/m^2)				
< 18.5	155 (3.8)	0.3–4.3	62 (2.5)	1.2–3.1

CI: confidence interval

[a] Family income expressed in local currency and converted into a multiple of minimum wage (R$788,00).

[b] Family history of diabetes mellitus. Variable with highest values of missing information (n = 675).

Variables	Perinatal sample		Eligible mothers	
18.5 - < 25.0	1037 (49.3)	47.8–50.8	1150 (47.5)	45.5–49.5
25.0 - < 30.0	1160 (28.1)	26.7–29.4	717 (29.6)	27.8–31.4
≥ 30.0	778 (18.8)	17.6–20.0	490 (20.2)	18.6–21.8
Parity				
1	2114 (49.6)	48.0–51.0	1298 (52.7)	50.7–54.6
2	1315 (30.8)	29.4–32.2	780 (31.7)	29.8–33.5
3	472 (11.0)	10.1–12.0	242 (9.8)	8.6–11.0
≥ 4	367 (8.6)	7.7–9.4	142 (5.8)	4.8–6.6
Family History of GDM[b]				
No	1707 (55.9)	54.2–57.8	993 (55.5)	53.2–57.8
Yes	1345 (44.1)	42.2–45.8	795 (44.4)	42.2–46.7
Smoke				
No	3553 (83.3)	82.1–84.3	2132 (86.6)	85.2–87.9
Yes	714 (16.7)	15.6–17.8	330 (13.4)	12.1–14.8

CI: confidence interval

[a] Family income expressed in local currency and converted into a multiple of minimum wage (R$788,00).

[b] Family history of diabetes mellitus. Variable with highest values of missing information (n = 675).

Women eligible for this study did not differ from women participating in the perinatal study of C2015 regarding the characteristics analysed (Table 1).

Of all women in the analysed sample (N = 2463), 69.7% were exposed to iron supplementation in the first and / or second trimester of pregnancy. The prevalence of GDM was higher among older pregnant women (12.8%), less educated (13.7%), with family income between 1.1 and 3.0 minimum / monthly salaries (10.2%). Pre-pregnancy BMI > = 30 (16.9%), who had 4 or more children (12.6%) and with a family history of diabetes (12.5%) (Table 2).

Table 2

Prevalence of gestational diabetes mellitus (GDM) according to independent variables (N = 2463). 2015 Pelotas (Brazil) Birth Cohort.

Variables	**Prevalence of DMG**			
	N	**%**	**95%CI**	**p-value[a]**
Age				< 0.001
≤ 19	6	2,1	0.9–4.6	
20–29	84	7.1	5.7–8.7	
30–46	128	12.8	10.8–15.1	
Skin colour				0.202
White	156	8.4	7.1–9.7	
Black	35	11.4	8.3–15.6	
Others	27	9.2	6.4–13.2	
Schooling (years)				0.004
≤ 4	23	13.7	9.2–19.8	
5–8	37	7.1	5.1–9.6	
9–11	95	10.6	8.7–12.8	
≥ 12	63	7.2	5.6–9.1	
Family income (minimum wages)[b]				0.002
≤ 1	19	8.5	5.5–13.0	
1.1–3.0	110	10.2	8.6–12.2	
3.1–6.0	68	9.9	7.9–12.4	
6.1–10.0	8	4.2	2.1–8.1	
> 10.0	4	2.4	0.9–6.3	

CI: confidence interval

[a] p value of chi-square test

[b] Family income expressed in local currency and converted into a multiple of minimum wage (R$788,00)

[c] Family history of diabetes mellitus gestational. Variable with highest values of missing information (n = 675).

Variables	Prevalence of DMG			
Pre-pregnancy body mass index (kg/m²)				< 0.001
< 18.5	1	1.6	0.2–11.1	
18.5 - <25.0	61	5.3	4.1–6.7	
25.0 - <30.0	70	9.7	7.7–12.1	
≥ 30.0	83	16.9	13.8–20.5	
Parity				< 0.001
1	83	6.4	5.1–7.8	
2	87	11.2	9.1–13.5	
3	30	12.4	8.7–17.2	
≥ 4	18	12.6	8.0–19.3	
Family History of GDM[c]				< 0.001
No	77	7.8	6.2–9.6	
Yes	100	12.5	10.4–15.1	
Smoke				0.644
No	191	8.9	7.8–10.2	
Yes	27	8.1	5.6–11.6	
Iron supplementation				0.626
No	68	9.3	7.4–11.5	
Yes	146	8.7	7.4–10.1	
Total	214	8.8	7.7–10.0	

CI: confidence interval

[a] p value of chi-square test

[b] Family income expressed in local currency and converted into a multiple of minimum wage (R$788,00)

[c] Family history of diabetes mellitus gestational. Variable with highest values of missing information (n = 675).

The prevalence of self-reported GDM in the entire cohort (N = 4270) was 8.5% (95% CI 7.6; 9.3) and among those eligible for this study was 8.8% (95% CI 7.7 ; 10.0), being 8.6% (95% CI 7.3 ; 10.0) among exposed and 9.2% (95% CI 8.9 ; 9.2) among those not exposed to iron supplements (Table 2).

The use of iron salts in the first or second gestational trimester showed no positive association with GDM both in the crude analysis (OR = 0.9 95% CI 0.6; 1.3) and in the adjusted analysis for skin colour, age, education, family income, pre-gestational BMI, parity, family history of diabetes mellitus and smoking during pregnancy (OR = 1.1 95% CI 0.8; 1.5) (Table 3).

Table 3
Association between iron salt supplementation and gestational diabetes mellitus among non-anemic women. 2015 Pelotas (Brazil) Birth Cohort.

Iron supplementation	**Crude**		**Adjusted [a]**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Non-anaemic pregnant women up to 24th weeks (N = 2463)		0.509		0.420
No	Reference (1.0)		Reference (1.0)	
Yes	0.9 (0.7–1.3)		1.1 (0.8–1.6)	
Non-anaemic pregnant women up to 12th weeks (N = 2559)		0.631		0.405
No	Reference (1.0)		Reference (1.0)	
Yes	1.1 (0.8–1.6)		1.2 (0.8–1.7)	

OR: odds ratio

[a] Model adjusted for skin color, age, education, family income in minimum wages, pre-gestational BMI, parity, smoking during pregnancy, family history of diabetes mellitus.

A subset of analyses was performed for data corresponding to the first trimester of pregnancy (up to 12th weeks). Results were similar from those derived from the main analyses (including the first and/or second trimester (adjusted OR = 1.2 95% CI 0.8; 1.7) (Table 3).

Discussion

This study showed that, among non-anemic women, prophylactic use of iron in the first and/or second trimester of pregnancy was not an independent risk factor for the development of GDM

Published evidence on this subject is controversial. Previous observational studies have suggested that higher stores of iron might be associated with glucose metabolism disorders and an increase in the risk of GDM(19–24). This relation is biologically plausible, because iron has a high capacity of oxirreduction and its free form can catalyze the formation of free radicals, causing cell damage, also known as oxidative stress. Therefore, other suggested mechanism involves the formation of hidroxil radical which can damage the cell membranes of pancreatic ß cells, affecting insulin synthesis and secretion associated with pregnancy-induced insulin resistance(25, 26). Also, the excess of iron deposition in the muscle may decrease glucose uptake (26). However, three randomized controlled trials, performed in hospitals and primary care services in China (N = 1164)(27), Finland (N = 2912)(28) and United Arab Emirates (N = 960)(29), found no significant difference in the incidence of GDM between control and experimental women. The daily iron dose in the experimental group ranged from 30mg to 60mg administered during the first and second gestational trimesters (28–30). In the control group two studies used placebo (28, 30) and one used a lower dosage of iron and a frequency of use lower than the experimental group (29). It should be noted that one of the randomized clinical trials cited (27) reported poor adherence to supplementation, which is a reality among pregnant women, mainly due to the undesirable adverse effects of iron supplementation (31), a fact that may alter the results of this and other researches, underestimating the real effect of this compound.

In our study no differences were found in the prevalence of GDM between women exposed and not exposed to the supplement, as in the study of Chan et al., 2009(27), who did not find increased incidence of GDM in the exposed group. The analysis of the study association may be limited due to lack of information regarding dosage, adherence, frequency of use and exposure time. Dosage information would be useful for qualifying the exposure variable (use of iron salts), considering "yes" only those compounds with prophylactic dosage. Knowledge of adherence to iron salt compounds would allow a better selection of women eligible for the study, and exposure time would be useful for estimating dose-response effect.

Regardless of the findings concerning the occurrence of GDM and iron use, it is a fact that GDM has been increasing in several countries as a result of population growth, increased maternal age, lack of physical activity and, especially, the increased prevalence of obesity (3, 32), and our findings confirm this trend, presenting prevalence of self-reported gestational diabetes almost three times higher than (8.5%; IC = 7.8 ; 9.6) another birth cohort study conducted in the year 2004, also in the city of Pelotas, with 4231 pregnant women, which found a self-reported prevalence of 3.0% gestational diabetes (95% CI: 2.53 ; 3.64)(33). It is known that there are many divergences between the diagnostic criteria used for GDM, but between 2004 and 2015 there were no changes in the diagnostic test cut-offs in the recommendations from Brazilian Ministry of Health (12, 34).

Among the limitations of this study, it should be noted that many pregnant women had only one or two hemoglobin results in the antenatal card, thus, pregnant women who had only one recorded hemoglobin test whose result was normal (non-anaemic), were eligible for our study. However, they may have developed anaemia later and such information was not registered in the card. On the other hand, the use of information from antenatal records completed by health professionals who followed this pregnant women was a positive aspect and considered indispensable for the definition of women eligible for the study, since these results enabled the identification of non-anemic pregnant women according to the gestational trimester, which guaranteed the temporality of the study association.

Information on GDM diagnostic and iron use was self-reported only, which can be considered other limitations of this study. Furthermore, the control variable “family history of diabetes”, was collected only from the third month of the 24-month follow-up of the children, which resulted in a high number of missing information (27.4%).

Among the positive aspects, we highlight the fact that all pregnant women who had a hospital delivery in the municipality were interviewed within one year, and the small number of refusals, which allows the generalization of the results to other pregnant women under the same conditions of our sample.

Conclusions

Our study showed that the use of iron supplementation in non-anaemic pregnant women was not related with the development of GDM, which meets current national and international guidelines, whose recommendation is the routine supplementation to all pregnant women as soon as they start antenatal care to prevent iron deficiency anaemia.

List Of Abbreviations

Gestational diabetes mellitus (GDM)

World Health Organization (WHO)

Body mass index (BMI)

Declarations

Ethics approval and consent to participate: The Federal University of Pelotas, School of Physical Education Ethics Committee, approved the study protocol (approval number 522.064). All mothers signed an informed consent form before being interviewed. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication: Not applicable.

Availability of data and materials: Due to confidentiality restrictions related to the ethics approval for this study, no identifying information about participants may be released. Dataset without identification used during the current study are available from the corresponding author on reasonable request.

Competing interests: none to declare

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Author Contributions: conceptualization, VIAM, MPTS, TSDP and ADB; methodology, VIAM, MPTS, SSM, BHL and ADB; formal analysis, VIAM, MPTS, RB and ADB; writing—original draft preparation, VIAM; writing—review and editing, VIAM, MPTS, TSDP, MSF, SSM, BHL, RB and ADB; supervision, MPTS, TSDP and ADB; project administration, ADB and MFS. All authors have read and approved the manuscript.

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Figures

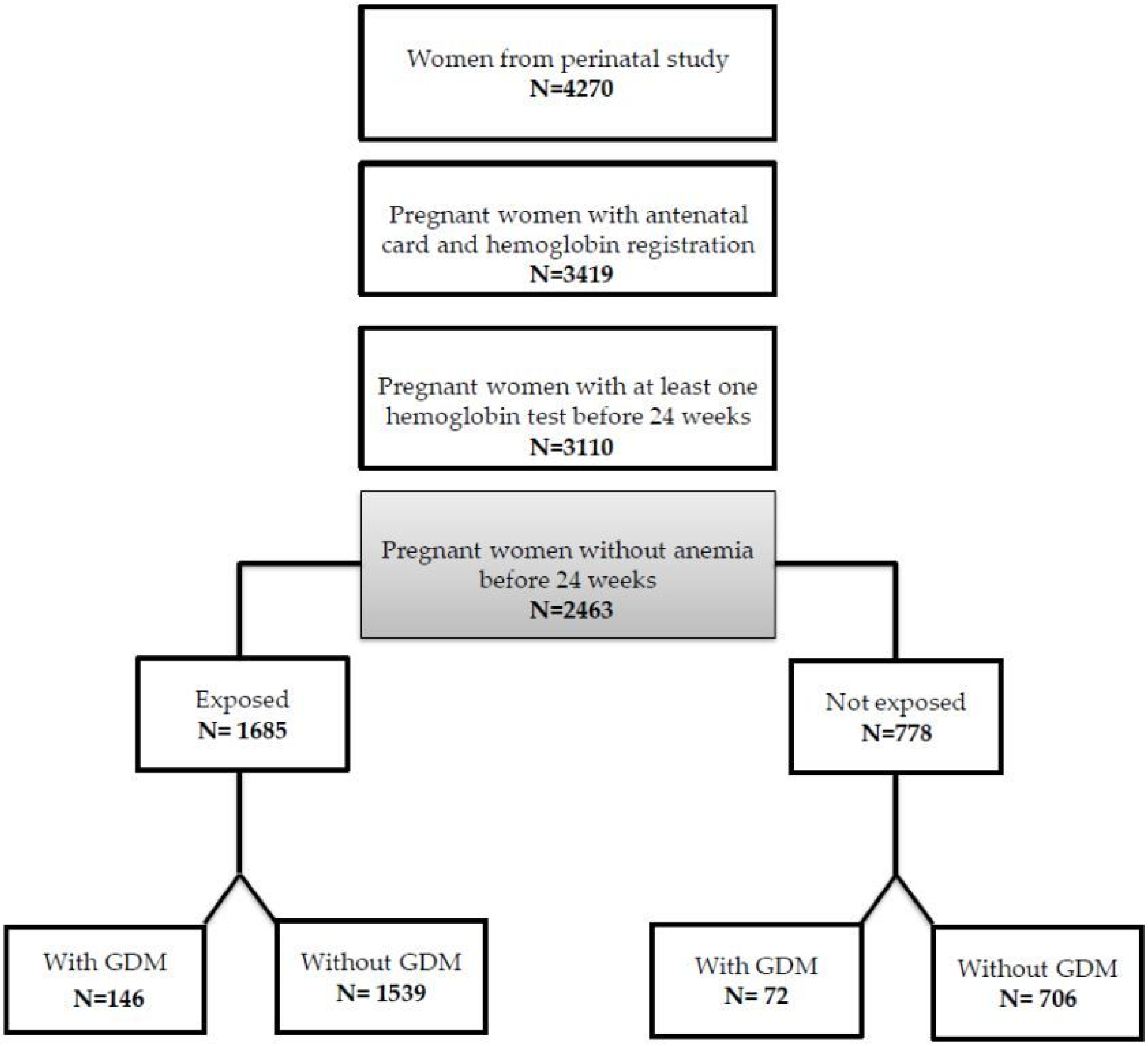

Figure 1

Flowchart of the study population of eligible women. 2015 Pelotas (Brazil) Birth Cohort.