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ORIGINAL ARTICLE

Diseases during pregnancy in a large unselected South American sample

Prevalência de doenças durante a gravidez em uma grande amostra sul-americana não selecionada

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ABSTRACT

Objective: Our aim was to describe the prevalence of diseases during pregnancy and the association between fetal exposure to the most frequent maternal diseases and the risk of preterm (PTB) and/or small for gestational age (SGA) newborns in an unselected sample of women who gave birth in South American countries. **Methods:** We conducted a descriptive, cross-sectional study including 56,232 mothers of non-malformed infants born between 2002 and 2016, using data from the Latin American Collaborative Study of Congenital Malformations (ECLAMC). Diseases with higher- than-expected PTB/SGA frequencies were identified. Odds ratios of confounding variables for diseases and birth outcomes were calculated with a multivariable logistic regression. **Results:** Of the 14 most reported diseases, hypertension, genitourinary infection, epilepsy, hypothyroidism, diabetes, and HIV/AIDS showed higher PTB and/or SGA frequencies. Advanced and low maternal age, previous fetal loss, low socioeconomic level, and African-American ancestry were associated with PTB, while advanced maternal age, primigravidity, previous fetal loss, low socioeconomic level, and African-American ancestry were associated with SGA. After adjusting for the associated variables, the identified illnesses maintained their association with PTB and all, except epilepsy, with SGA. **Conclusion:** The description of an unselected population of mothers allowed identifying the most frequent diseases occurring during gestation and their impact on pregnancy outcomes. Six diseases were associated with PTB and two with SGA newborns. To the best of our knowledge, there are no similar reports about women not intentionally selected by specific diseases during pregnancy in South American populations.

Keywords: Pregnancy. Disease. Pregnancy complications, infectious. Chronic disease. Infant, small for gestational age. Infant, premature.

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CONFLICT OF INTERESTS: nothing to declare.

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INTRODUCTION

Preterm birth (PTB), with an estimated 10.6% global rate and a 9.8% Latin-American prevalence[1], and small for gestational age (SGA), with a 27% prevalence in low-middle income countries and 13% in Latin America[2], are determining factors for perinatal morbi-mortality worldwide. They are also related to poor postnatal growth and diseases whose consequences may extend to late adulthood[3-5], as well as with a high burden due to prolonged interventions.

Fetal exposure to diseases occurring during pregnancy may increase the risk of PTB or SGA[6-8]. Chronic illnesses such as cardiac and respiratory diseases, cancer, and diabetes are the main causes of worldwide mortality and affect one in 20 pregnant women[9].

Infectious diseases during pregnancy are still common especially in developing countries[10,11]. Fetuses can be affected directly by the infectious agent or indirectly by maternal infection consequences, leading to congenital malformations, miscarriages, fetal death, PTB, or SGA. The impact varies according to the specific agent and exposure level, gestational age, the mother's immune status, maternal and fetal genetic susceptibility, and interaction among factors.

Furthermore, persistent or recurrent infections probably explain many repetitive spontaneous preterm births[12]. Similarly, disorders leading to medically induced preterm deliveries, such as diabetes or hypertension, frequently persist between pregnancies.

The aim of this study, in addition to a literature review, was to present the prevalence of the most frequent diseases and of PTB and SGA in a large South American sample of women who reported having been ill during gestation. While most previous studies have focused on specific diseases, we found no similar reports where women were not intentionally selected by a particular disease.

METHODS

The study sample comprised database registries of the Latin American Collaborative Study of Congenital Anomalies (ECLAMC), a program dedicated to the research of birth defects through a network of maternity hospitals. Data on socioeconomic and demographic characteristics, previous birth outcomes, and prenatal factors were obtained from medical records and by interviewing the mothers of malformed infants and their controls (defined as the non-malformed infant of the same sex, born at the same hospital, immediately after the malformed one) before discharge. A detailed description of ECLAMC's registry and methodology has been previously published[13].

In this observational, cross-sectional, hospital-based study, which only included mothers of the non-malformed control infants, birth registries from 90 maternity hospitals of 10 South American countries were used, over a total of 1,962,767 births, between 2002 and 2016. Stillborn and multiple births were excluded. From 56,232 mothers of non-malformed newborns, 16,176 (28.8%) reported having been ill during pregnancy at any gestational age, while 40,056 reported no illnesses and were used for comparison. Of the 16,176 mothers, we included 10,928 whose illnesses (a total of 16,052 occurrences) had a ≥2/1000 prevalence which was calculated as the number of mothers with each disease over the total number of mothers. The sample size was calculated for an estimated 5% prevalence error and a 95% confidence. All included illnesses were equally considered, with or without diagnostic confirmation procedures. The remaining 5,248 mothers had less prevalent or unspecified diseases, or conditions not considered as diseases such as vomiting, headache, threatened abortion, or mental retardation, and were not included in the study.

Exposure

Maternal diseases

Fourteen diseases had the required prevalence and were included in this study: hypertension (comprising preeclampsia and gestational and chronic hypertension), anemia, asthma, diabetes, hypothyroidism, Chagas disease (endemic parasitic disease frequent in South American poor rural environment), epilepsy, obesity, urinary tract infection (including pyelonephritis), influenza, vaginal infection, toxoplasmosis, HIV/AIDS, and syphilis. Two or more coexisting illnesses were considered individually. Around half of the mothers with influenza, diabetes, and hypertension had one or more additional diseases while Chagas disease, toxoplasmosis, HIV/AIDS, and syphilis occurred as single illnesses in around 90% of cases.

Confounding variables

A potential confounding effect was evaluated for the following variables:

1. Maternal age (<20 and ≥30 years);
2. Gravidity (primigravidity and multigravidity >3);
3. Previous fetal loss (stillbirth or miscarriage);
4. Socioeconomic level (low and high according to a standardized scale of maternal and paternal schooling and occupation);
5. Few prenatal visits (≤5); and
6. Newborn ancestry (all ancestors Native American, African-American with any other ethnicity, and all ancestors Latin-European).

Outcomes

Newborns were classified according to their birth weight and gestational age into three growth categories:

1. AB: adequate at birth (gestational age ≥37 weeks, birth weight ≥2500g),
2. PTB: preterm birth (gestational age <37 weeks, birth weight >10th percentile for gestational age), and
3. SGA: small for gestational age (any gestational age, birth weight <10th percentile for gestational age).

Large for gestational age (LGA) newborns which comprised less than 5% of the total population of newborns were included in the AB category.

Statistical analysis

Prevalence and 95% confidence interval (95%CI) of PTB and SGA for each disease were obtained over the total number of mothers with that particular disease. The diseases with higher-than-expected PTB or SGA frequencies were identified.

The expected number of cases for each disease in categories PTB and SGA was calculated based on the frequency of observed infants born to mothers without disease for each respective category. The observed/expected ratio and its 95%CI was estimated for a Poisson distribution.

A multinomial logistic regression was applied to estimate the confounding effect of the included variables for each of the 14 diseases.

Odds ratios (OR) and their 95%CI were obtained to identify variables associated with PTB or SGA.

A logistic regression was applied to adjust the risk for PTB or SGA of diseases with significantly higher observed than expected PTB or SGA prevalence. For each disease, it included the confounding variables significantly associated both with that disease and with the adverse perinatal outcome.

Ethics approval

The study protocol was approved by the Ethics Committee "Centro de Educación Médica e Investigaciones Clínicas (CEMIC)" (DHHS-IRB #1745, IORG #1315). Written signed informed consents were obtained from all subjects participating in the ECLAMC program before data collection. All data were fully anonymized prior to their utilization.

RESULTS

The ECLAMC registry covers all South American countries except the Guyanas. From an unselected population of postpartum women, around 30% reported having suffered illnesses during pregnancy; of these, approximately 70% had had one or more of the 14 most frequent diseases. The prevalence of diseases can be found in Table 1 and the prevalence of PTB and SGA by disease is available in Table 2.

Table 3 presents the association of confounding variables with PTB and SGA in women without diseases during

Table 1. Prevalence of diseases during pregnancy in a sample of 56,232 South American women.

Disease	n	%	95%CI
No disease	40,056	71.2	70.9–71.6
Urinary infection	7,292	13.0	12.7–13.3
Influenza	2,102	3.7	3.6–3.9
Hypertension	1,766	3.1	3.0–3.3
Diabetes	903	1.6	1.5–1.7
Anemia	880	1.6	1.5–1.7
Asthma	842	1.5	1.4–1.6
Vaginal infection	657	1.2	1.1–1.3
Hypothyroidism	544	1.0	0.9–1.1
Toxoplasmosis	223	0.4	0.3–0.5
HIV/AIDS	206	0.4	0.3–0.4
Syphilis	190	0.3	0.3–0.4
Chagas disease	155	0.3	0.2–0.3
Epilepsy	154	0.3	0.2–0.3
Obesity	138	0.3	0.2–0.3

CI: confidence interval.

Table 2. Prevalence of preterm birth and small for gestational age by disease in a sample of 56,232 South American women.

	Total	PTB				SGA			
	n	n	% (95%CI)	E	O/E (95%CI)	n	% (95%CI)	E	O/E (95%CI)
No disease	40,056	2,498	6.2 (6.0–6.5)	--	--	2,338	5.8 (5.6–6.1)	--	--
Urinary infection	7,292	601	8.2 (7.6–8.9)	454.7	1.3 (1.2–1.4)	461	6.3 (5.8–6.9)	425.6	1.1 (1.0–1.2)
Influenza	2,102	141	6.7 (5.8–7.9)	131.1	1.1 (0.9–1.3)	94	4.5 (3.6–5.4)	122.7	0.8 (0.6–0.9)
Hypertension*	1,766	230	13.0 (11.4–14.7)	110.1	2.1 (1.8–2.4)	236	13.4 (11.8–15.0)	103.1	2.3 (2.0–2.6)
Diabetes	903	83	9.2 (7.4–11.3)	56.3	1.5 (1.2–1.8)	29	3.2 (2.2–4.6)	52.7	0.6 (0.4–0.8)
Anemia	880	46	5.2 (3.9–6.9)	54.9	0.8 (0.6–1.1)	42	4.8 (3.5–6.4)	51.4	0.8 (0.6–1.1)
Asthma	842	58	6.9 (5.3–8.8)	52.5	1.1 (0.8–1.4)	47	5.6 (4.1–7.4)	49.1	1.0 (0.7–1.3)
Vaginal infection	657	71	10.8 (8.5–13.4)	41.0	1.7 (1.4–2.2)	42	6.4 (4.6–8.5)	38.3	1.1 (0.8–1.5)
Hypothyroidism	544	53	9.7 (7.4–12.5)	33.9	1.6 (1.2–2.0)	27	5.0 (3.3–7.1)	31.8	0.9 (0.6–1.2)
Toxoplasmosis	223	10	4.5 (2.2–8.1)	13.9	0.7 (0.3–1.3)	12	5.4 (2.8–9.2)	13.0	0.9 (0.5–1.6)
HIV/AIDS	206	19	9.2 (5.6–14.0)	12.8	1.5 (0.9–2.3)	25	12.1 (8.0–17.4)	12.0	2.1 (1.4–3.1)
Syphilis	190	12	6.3 (3.3–10.8)	11.8	1.0 (0.5–1.8)	9	4.7 (2.2–8.8)	11.1	0.8 (0.4–1.5)
Chagas disease	155	2	1.3 (0.2–4.5)	9.7	0.2 (0.0–0.7)	5	3.2 (1.1–7.4)	9.0	0.6 (0.2–1.3)
Epilepsy	154	16	10.4 (6.1–16.3)	9.6	1.7 (1.0–2.7)	15	9.7 (5.6–15.6)	9.0	1.7 (1.0–2.8)
Obesity	138	12	8.7 (4.6–14.7)	8.6	1.4 (0.7–2.4)	10	7.2 (3.5–12.9)	8.1	1.2 (0.6–2.3)

PTB: preterm birth; SGA: small for gestational age; CI: confidence interval; E: expected value; O/E: observed/expected values. *Hypertension includes preeclampsia, and gestational and chronic hypertension.

Table 3. Association of confounding variables with preterm birth and with small for gestational age in women without diseases during pregnancy.

	PTB		SGA	
	OR	95%CI	OR	95%CI
Maternal age <20	1.3	1.1–1.6	1.1	0.9–1.3
Maternal age ≥30	1.1	0.9–1.4	1.2	1.0–1.4
Primigravidity	1.1	0.9–1.3	1.5	1.3–1.8
Multigravidity	1.0	0.9–1.1	1.0	0.8–1.2
Previous fetal loss	1.4	1.2–1.7	1.4	1.2–1.7
Low socioeconomic level	1.2	1.0–1.4	1.3	1.1–1.6
High socioeconomic level	1.2	0.9–1.5	1.0	0.8–1.3
Few prenatal visits	1.1	0.9–1.3	1.1	0.9–1.3
African-American ancestry	1.6	1.2–2.3	1.7	1.3–2.2
Native ancestry	0.9	0.7–1.2	0.9	0.6–1.3
Latin-European ancestry	1.0	0.7–1.4	1.1	0.7–1.7

PTB: preterm birth; SGA: small for gestational age; OR: odds ratio; CI: confidence interval.

pregnancy and Table 4 shows the significant associations between these variables and the most frequently reported diseases. Four confounding variables showed association with PTB (maternal age <20, previous fetal loss, low socioeconomic level, and African-American ancestry), three of which (previous fetal loss, low socioeconomic level, and African-American ancestry), plus primigravidity and maternal age ≥30, were also associated with SGA.

Six of the 14 diseases were significantly associated with PTB (urinary infection, hypertensive disorders, diabetes, vaginal infections, hypothyroidism, and epilepsy) and three with SGA newborns (hypertension, HIV/AIDS, and epilepsy). After adjusting for the confounding variables, all identified illnesses maintained their association with PTB and all, except epilepsy, with SGA (Table 5).

DISCUSSION

Women may suffer from acute and/or chronic diseases during pregnancy and fetal exposure can increase the risk of adverse outcomes; so far, literature reports on chronic diseases prevalence during pregnancy and their outcomes are discordant. For example, Kersten et al.[14] reported that at least one of every five pregnant women in a sample of 5,320 subjects suffered from a chronic disease and Gogoi and Unisa[15] informed that 50% of pregnant women attending a tertiary hospital from Mumbai (Maharashtra, India) had some sort of chronic disease, with anemia as the most frequent, while Jølving et al.[16], using nationwide Danish data on more than 1.3 million childbirths, estimated an 8.5% chronic disease prevalence. Variables such as study design, lack of standardized diagnostic procedures, and regional differences could, among others, explain the different rates.

The approximately 10% prevalence of chronic diseases in this study, is close to the values found by Jølving

Table 4. Significant associations between confounding variables and diseases.

Disease	n	Confounding variables	OR	95%CI
Urinary infection	7,292	Primigravidity	1.2	1.0–1.3
		Previous fetal loss	1.3	1.1–1.5
		African-American ancestry	1.6	1.3–2.2
Influenza	2,102	Previous fetal loss	1.4	1.0–1.0
Hypertension*	1,766	Maternal age ≥30	2.4	2.0–2.9
		Low socioeconomic level	1.4	1.1–1.7
Diabetes	903	Maternal age ≥30	3.8	2.6–5.4
Anemia	880	Maternal age <20	1.6	1.1–2.5
Asthma	842	Latin-European ancestry	1.8	1.1–3.1
Vaginal infection	657	Native ancestry	1.7	1.0–2.9
Hypothyroidism	544	Maternal age ≥30	2.7	1.6–4.6
		Primigravidity	1.5	1.1–2.1
		High socioeconomic level	1.8	1.3–2.5
		Previous fetal loss	1.4	1.0–2.0
Toxoplasmosis	223	Multigravidity	2.2	1.6–3.0
		Low socioeconomic level	1.5	1.2–1.9
HIV/AIDS	206	Multigravidity	2.0	1.4–2.8
		Low socioeconomic level	1.5	1.0–2.3
		Few prenatal visits	2.0	1.3–2.9
		African-American ancestry	5.0	1.9–13.4
Syphilis	190	Low socioeconomic level	1.5	1.0–2.2
Chagas disease	155	Maternal age ≥30	1.8	1.2–2.7
		Low socioeconomic level	1.7	1.2–2.7
		Few prenatal visits	2.2	1.5–3.4
		Native ancestry	4.5	1.6–12.6
Epilepsy	154	Maternal age ≥30	1.9	1.3–2.9
		Previous fetal loss	2.3	1.5–3.5
Obesity	138	Maternal age ≥30	2.5	1.9–3.4

OR: odds ratio; CI: confidence interval. *Hypertension includes preeclampsia, and gestational and chronic hypertension.

Table 5. Adjusted risk for preterm birth and small for gestational age by disease.

	OR	95%CI	ORadj	95%CI
PTB				
Hypertension*	2.0	1.8–2.3	2.1	1.8–2.4
Vaginal infection	1.7	1.4–2.2	1.7	1.4–2.2
Epilepsy	1.7	1.1–2.7	1.7	1.0–3.0
Hypothyroidism	1.6	1.2–2.0	1.5	1.1. 2.0
Diabetes	1.5	1.2–1.8	1.4	1.1–1.8
Urinary infection	1.3	1.2–1.5	1.3	1.2–1.5
SGA				
Hypertension*	2.3	2.0–2.6	2.4	2.1–2.8
HIV/AIDS	2.1	1.4–3.0	1.8	1.2–2.6
Epilepsy	1.7	1.0–2.7	1.4	0.7–2.8

OR: odds ratio crude; CI: confidence interval; ORadj: adjusted odds ratio with a Poisson regression model; PTB: preterm birth; SGA: small for gestational age. *Hypertension includes preeclampsia, and gestational and chronic hypertension.

et al.[16] and both studies identified the same most prevalent diseases (hypertension, diabetes, thyroid disorders, and epilepsy).

Hypertensive disorders

Around 3% of the women in our sample reported having been hypertensive during pregnancy and, in agreement with most of the literature, almost 30% of their newborns were either preterm or SGA. Their risk of having a SGA infant almost doubled that of non-hypertensive mothers. Hypertensive disorders, mainly preeclampsia, are a widely recognized cause of SGA and probably deserve no further discussion. However, differences have been described between early and late onset preeclampsia (before and after 34 gestational weeks, respectively), the former leading to SGA and the latter, often associated with maternal diabetes and obesity, too LGA infants[17].

On the other hand, Bramham et al.[7] reported an almost three-fold PTB risk in mothers with chronic hypertension based on a meta-analysis that included more than 70,000 pregnant women from 25 countries. Similarly, in a cohort study of 7,000 mothers, and after adjusting for more than ten confounding variables, Shen et al.[18] demonstrated a PTB risk almost twice as high for gestational hypertension and seven-fold for preeclampsia.

However, and although hypertensive disorders, mainly preeclampsia, could *per se* lead to spontaneous PTB through, for example, abruption of the placenta, induced preterm delivery to avoid severe maternal complications seems to be the major cause of the reported PTB excess. It has been estimated that about one third of PTB are medically induced and that preeclampsia is its primary indication[19]. Using cesarean section as a proxy for induced delivery, we compared its rate between hypertensive and healthy women. It was significantly higher in the former than in the latter (56% vs. 35%) and even higher when the comparison was done between women who had delivered prematurely (68% vs. 41%). Other authors observed similar rate differences[7,18].

Diabetes

In our sample, 1.6% of the mothers were diabetic and almost 10% of their deliveries were preterm. While some authors such as Köck et al.[6] showed that spontaneous PTB was associated with diabetes, others considered that the most likely cause was medically induced PTB because of coexisting preeclampsia[20]. Results obtained by other authors were inconsistent[21,22].

On the other hand, and as universally accepted, in our sample of diabetic mothers the prevalence of SGA infants was lower than expected. Similar results were obtained by other authors who also described higher rates of large babies in women with impaired glucose tolerance[3].

In opposition, however, some authors hypothesized that diabetic vasculopathy leads to impaired fetal growth. Boghossian et al.[23] observed an excess of SGA newborns among extremely preterm infants born to pregestational diabetic mothers (probably with diabetes types 1 or 2) when compared with those who had started using insulin during gestation (probably type 2 and gestational diabetes).

While Skaznik-Wikiel et al.[24] reported that the rate of SGA infants in mothers with pregestational diabetes was not higher than expected, Shefali et al.[25], although with a small sample size, observed a higher frequency of LGA infants born to mothers with gestational diabetes than to non-diabetic control mothers.

In our sample, no distinction could be established between different types of diabetes. However, when reviewing the medication reports, only 10% of all diabetic mothers had used insulin during gestation. On this basis we could assume a higher proportion of gestational than pregestational diabetes which might explain the lack of SGA infants born to these mothers.

Hypothyroidism

Hypothyroidism, which is almost ten times more frequent in women than in men, has been shown to affect 1.5–4.0% of pregnant women[26,27]. Its rather low prevalence (1%) in our sample could be due to a number of factors such as incomplete reporting because of unawareness in subclinical cases, lack of diagnosis in women without prenatal control, and preferential reporting of women whose illness was diagnosed before being pregnant, among others.

Globally, and especially in developing countries, environmental iodine deficiency is the most common cause of thyroid disorders, while chronic autoimmune thyroiditis (Hashimoto's disease) is the main cause of primary hypothyroidism in iodine-sufficient areas[28,29].

Literature reports disagree regarding the association between clinical or subclinical hypothyroidism and adverse pregnancy outcomes. While Cleary-Goldman et al.[30], among others, concluded that maternal thyroid hypofunction is not associated with a consistent pattern of adverse outcomes, in a prospective population-based study from China, involving 1,017 pregnant women, Su et al.[31] showed that subclinical hypothyroidism was associated with PTB; conversely, Plowden et al.[32] found no such association. Abalovich et al.[33] showed that the pregnancy outcome of hypothyroid women did not depend on whether their disease was overt or subclinical, but on the received treatment. They also showed that if hypothyroid women, even with normal thyroid function, were not adequately treated, they had an increased risk of spontaneous abortion. In our sample, nearly 40% of the hypothyroid women, whose deliveries were preterm, informed having received no treatment and 26% of them reported a previous miscarriage. However, it could not be established if during that previous pregnancy these mothers had been hypothyroid and if they were medicated.

Stagnaro-Green et al.[34] suggested that anti-thyroid antibodies, as part of a generalized autoimmune imbalance, could be responsible for the eventually observed adverse outcomes while Kiran et al.[35] found no association between thyroid antibodies and prematurity in hypothyroid women.

Epilepsy

With the exclusion of the teratogenic effects of antiepileptic drugs, the results on pregnancy outcomes of epileptic women reported in the literature are contradictory. Crump et al.[36] found an association of epilepsy with PTB that persisted when antiepileptic drugs were used. Contrarily, other authors found that the risk of adverse outcomes increased with the use of antiepileptic drugs[37,38]. Reports from MacDonald et al.[39], who also observed an increased PTB risk, lacked information on the use of antiepileptic medication. Kilic et al.[40] found a 25% increased PTB risk in non-medicated epileptic mothers and considered that it represented early termination of pregnancy due to maternal seizures. The 0.27% prevalence observed in our study coincided with the 0.3–0.5% mentioned by MacDonald et al.[39] and we found a 30% higher PTB risk in epileptic mothers while, after adjusting for confounders, no association with low birth weight was observed. Fewer mothers from the PTB and SGA groups had used antiepileptic drugs when compared with the adequate at birth group; however, the differences did not reach statistical significance because of the small number of cases.

Furthermore, in our sample, half of the mothers from the PTB group had delivered through cesarean section but again the sample was too small to be conclusive about the possibility of induced deliveries.

Vaginal and urinary tract infections

Considering infectious diseases during pregnancy, Collier et al.[41] reported a prevalence of about 64% while in our study it was around 20%. Variations in the inclusion criteria are probably involved in the difference, for example, these authors included unspecified infections and fever with and without identified infection while in our sample, only those infections specifically mentioned by the mothers were considered. In coincidence with Sever et al.[42], influenza and vaginal and urinary tract infections were the most frequent self-reported diseases. It should however be taken into account that influenza is an unreliable diagnosis, often used as a general term for any unspecific cold.

The most common bacterial infections during pregnancy are those of the vaginal and urinary tract, and the chorioamnionitis, as a possible complication due to bacteria ascending into the amniotic cavity, is one of the most frequent factors associated with PTB[43].

Leitich and Kiss[44] reported PTB in approximately 10 to 15% of women suffering from bacterial vaginosis and a two-fold PTB risk based on a meta-analysis with 32 studies that included 30,518 patients. The related urinary tract infection (UTI) has also been associated with PTB although some studies have not confirmed this association[45,46].

In our study, the PTB prevalence of mothers with vaginal infections coincided with the published data, while 8.2% PTB prevalence observed in UTI patients was lower than the reported 15 to 32.9%[45,47]. African-American ancestry, often related to low socioeconomic level and less prenatal care, was a risk factor for women with UTI in our sample. This fact could suggest a lack of diagnosis of asymptomatic bacteriuria, which is a frequent UTI manifestation, and explain the difference between our results and those of published data[48]. On the other hand, overlapping of both infections, their coexistence, or perhaps their misdiagnoses should also be considered.

Many investigators have assumed that the strong evidence supporting the association between infection and increased PTB risk implied causation[43]. However, in general, antibiotic therapy of genitourinary tract infections has not reduced the PTB incidence. McClure and Goldenberg[49] considered the presence of abnormal vaginal flora as a simple marker of other risk factors. Results from other studies suggest interactions between genitourinary tract infections and genes linked to infectious/inflammatory/hormonal regulation processes that increase the PTB risk[50,51].

HIV/AIDS

In our sample, HIV/AIDS was the only maternal infection associated with SGA newborns. Around 12% of infants born to mothers with HIV/AIDS were SGA and the risk of these mothers for such an outcome was significant. Wedi et al.[52] reported similar results, although their sample consisted of 53,623 HIV mothers without antiretroviral therapy. We observed no differences after stratifying our sample by antiretroviral drugs treatment.

Kreitchmann et al.[8] have reported low birth weight or SGA and prematurity of infants born to HIV infected mothers in a study involving six South American countries. Similar results were reported by Delicio et al.[53] in a Brazilian study that included antiretroviral therapy and by Xiao et al.[54] in a meta-analysis of 52 cohort studies.

The association between immunosuppression and adverse pregnancy outcomes has been mentioned and HIV-related damage to the immune system was considered as the main cause of fetal growth restriction in pregnant HIV infected women[55]. Other risk factors are HIV replication and cytokine profile in the placenta affecting its function and the effect of antiretroviral drugs on systemic or local genital tract immunology or on systemic cytokines exacerbating hypertensive disorders[54,56]. In a study on 413 HIV-exposed but uninfected infants, Slyker et al.[57] identified several confounding variables associated with PTB or SGA such as maternal genital infection and cervical HIV-1 RNA load. The authors considered that the reduction of maternal genital HIV-1 replication could be a strategy to reduce the risk of adverse neonatal outcomes.

Strengths and limitations

The strength of the study is the large sample size comprising data gathered by trained health professionals that allowed making inferences about the risk of perinatal adverse events in South American populations. Additionally, our sample of mothers was unselected and thereby representative of the whole population while most published studies have focused on selected samples of women with specific diseases and their impact on pregnancy outcomes.

This study has some limitations. The ECLAMC program has good quality data but low territorial coverage, it is therefore inadequate to perform any regional analysis. Additionally, self-reporting implies a number of weaknesses such as memory bias when data are retrospectively obtained or lack of self-awareness of certain conditions, such as obesity considered as a disease, that leads to underreporting. Overreporting should also be considered for conditions such as influenza, a term which is often used when referring to any minor cold.

Moreover, each disease was evaluated individually, for this reason, in comorbidity cases, the one actually responsible for the adverse outcome could not be identified.

Some confounding variables that could act as risk factors such as a previous history of PTB, spontaneous or induced delivery, smoking, or alcohol intake were not considered, nor were socioeconomic or demographic characteristics of the regions under study. Medication as well as cesarean sections and previous abortions were not included as confounders and therefore, were not specifically analyzed. However, some findings on these variables that were not the result of a preconceived idea were obtained by reviewing the reports when relevant to support the discussion.

The database housing the used registries only allowed categorical information, therefore, clinical details, for example, chronic or acute forms of diseases such as syphilis or Chagas, could not be differentiated.

As a conclusion, taking into account the limitations mentioned above, the analysis of a large, unselected population of mothers in this study allowed us to evaluate the prevalence of the most frequent diseases during pregnancy and their impact on the considered outcomes in a South American population. Six diseases (urinary infection, hypertensive disorders, diabetes, vaginal infections, hypothyroidism, and epilepsy) were associated with PTB and two (hypertension and HIV/AIDS) with SGA newborns. These results may help clarify discordances found in the literature besides adding data to the scarce information available in South America.

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RESUMO

Objetivo: Descrever a prevalência de doenças durante a gravidez e a associação entre a exposição fetal às doenças maternas mais prevalentes e o risco de recém-nascidos prematuros (PP) e/ou pequenos para a idade gestacional (PIG) em uma amostra não selecionada de mulheres que deram à luz em países da América do Sul. **Métodos:** Estudo descritivo transversal que incluiu 56.232 mães de crianças não malformadas nascidas entre 2002 e 2016, utilizando dados do Estudo Colaborativo Latino-americano de Malformações Congênitas (ECLAMC). Foram identificadas as doenças com maior número de casos observado/esperado de PP/PIG. O esperado foi obtido dos controles sem doenças. *Odds ratios* para variáveis de confusão de doença e eventos ao nascimento foram calculadas usando regressão logística multivariada. **Resultados:** Das 14 doenças mais referidas, hipertensão, infecção geniturinária, epilepsia, hipotireoidismo, diabetes e HIV/AIDS apresentaram maiores frequências de PP e/ou PIG. Idade materna nos dois extremos, perda fetal prévia, baixo nível socioeconômico e ascendência afro-americana foram associados a PP, enquanto idade materna avançada, primigravidez, perda fetal prévia, baixo nível socioeconômico e ascendência afro-americana foram associados a PIG. Após ajuste para as variáveis associadas, as doenças identificadas mantiveram associação com PP e todas, exceto epilepsia, com PIG. **Conclusão:** A descrição de uma população não selecionada de gestantes possibilitou identificar as doenças mais frequentes e seu impacto nos resultados adversos na gravidez. Seis doenças foram associadas a PP e duas a recém-nascidos PIG. Até onde sabemos, não há relatos semelhantes sobre mulheres não selecionadas intencionalmente por doenças específicas durante a gravidez em populações sul-americanas.

Palavras-chave: Gravidez. Doença. Complicações infecciosas na gravidez. Doença crônica. Recém-nascido pequeno para a idade gestacional. Recém-nascido prematuro.

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