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Factors associated with miscarriage and perinatal mortality in women with HIV infection

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ABSTRACT

The purpose of this study was to evaluate risk factors associated with miscarriage (defined as the interruption of pregnancy before the 20th week of gestation) and perinatal mortality (defined as fetal death from the 21st week of pregnancy until neonatal stage, occurring until the first week of life) in HIV-infected pregnant women. This retrospective, cross-sectional study included HIV-infected pregnant women from Brazil aged between 18 and 47 years, who had miscarriage, vaginal delivery, or delivery by cesarean section. Data on miscarriage or perinatal mortality, sociodemographic characteristics, clinical conditions, and treatment were obtained. Statistical analyses included the use of binary logistic regression. In this cohort, the prevalence of miscarriage was 6.1% and the perinatal mortality rate was 4.0%. Risk factors for miscarriage included drug use (OR = 6.23; CI = 0.5 to 73.1), multiple gestation (OR = 3.06; CI = 0.9 to 10.9), and lack of prenatal care (OR = 18.42; IC = 3.9 to 87.6). Moreover, risk factors for perinatal mortality included drug use (OR = 1.03; IC = 0.9 to 1.1), vaginal delivery (OR = 5.56; CI = 1.2 to 26.1), and the absence of antiretroviral use during labor (OR = 17.77; CI = 3.9 to 81.8). In order to reduce the rates of miscarriage and perinatal mortality in HIV-infected pregnant women, actions aimed at eliminating drug use during pregnancy, ensuring adequate prenatal care, performing elective cesarean section delivery, and using antiretroviral medications during labor should be prioritized.

Keywords: Pregnant women, abortion, miscarriage, perinatal mortality, risk factors.

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INTRODUCTION

In Brazil, it is estimated that in 2012, approximately 12,177 pregnant women were infected with HIV; however, only 58.3% of these cases were notified. Of the total number of pregnancies in HIV-infected women, 1.8% resulted in miscarriages and 2% in perinatal mortality (Barcellos et al., 2009; Brasil, 2013).

There is evidence that 51 to 91% of pregnancies in women infected with HIV occurs in the absence of prenatal planning and monitoring, with a consequent reduction of avoidable risks (Holmes et al., 2012).

Risk factors associated with miscarriage, defined as the interruption of pregnancy before the 20th week of gestation, include high age, a low level of education, unemployment or unstable employment, low socioeconomic status, previous multiple gestation pregnancies, a high number of sexual partners, use of illicit drugs, and a low CD4+ T cell count (Gracia et al., 2005; Kim et al., 2012; Pilecco et al. 2014).

Risk factors associated with perinatal mortality, defined as fetal death from the 21st week of pregnancy until neonatal stage, occurring until the first week of life, include complications during labor, labor performed at home, low birth weight, maternal obesity, multiple gestation pregnancies, failure to comply with prenatal programs, and high viral load (Tachiweyika et al., 2011; Kim et al., 2012).

Women who get pregnant after being diagnosed with HIV infection are usually young, have few years of schooling, low sexual activity, limited use of contraception, a greater number of prior pregnancies, and induced abortions compared with women with HIV (Konopka et al., 2010; Villela et al., 2012).

The reduction in the rate of miscarriage and perinatal mortality is a major challenge for regional health services, governments, and the general society; the incidence was high and concentrated in regions with the most disadvantaged populations, having a low income. This situation reflects the social inequalities and timely unavailability of qualified health services in the affected countries (Schoeps et al., 2007; Santos et al., 2012).

Due to a lack of the epidemiological knowledge of miscarriage and perinatal mortality in HIV-positive pregnant women, studies are required to estimate the prevalence of and risk factors associated with perinatal mortality and abortion. Therefore, this research aims to assess the aforementioned factors in HIV-positive pregnant women.

METHODOLOGY

This retrospective, cross-sectional study of HIV-positive pregnant women was performed in the outpatient prenatal and high-risk Obstetric Centre and Puerperium Unit, Infectious Diseases Outpatient Clinic, and Pediatric Gynecologic University Hospital de Santa Maria, Brazil.

The study comprised a total population of 198 HIV-positive pregnant women during 2008 to 2012. Inclusion criteria were (a) HIV-positive pregnant women and (b) referral to the hospital due to abortion, vaginal birth, or cesarean section.

Data were collected from July to December 2013, and information was obtained by reviewing records in the information system on notifiable and reportable diseases on HIV-positive pregnant women and by the clinical records of HIV-seropositive women.

The dependent variable was the presence of abortion or perinatal mortality, while the independent variables included age (in years), education (in the study year), pregnancy (number of fetuses), individual notification of pregnancy (in which trimester of pregnancy was the current pregnancy reported to the health service), number of sexual partners (single or multiple), serological condition of the sexual partner (uninfected or infected by HIV), drug use (yes or no), compliance with prenatal program (yes or no), time of first prenatal appointment (first, second, or third trimester), time of HIV infection diagnosis (before prenatal, prenatal, or during pregnancy), use of antiretrovirals during pregnancy (yes or no), CD4+ T cell counts (cells/µl), viral load (copies/ml), clinical complications (anemia, premature labor, diabetes mellitus, or systemic hypertension), associated infections (hepatitis C, syphilis, toxoplasmosis, herpes, tuberculosis, urinary tract infection, or vaginal infection), type of delivery (vaginal or cesarean), use of antiretroviral prophylaxis during childbirth (yes or no), and performing a rapid test for detecting HIV infection before delivery (yes or no).

Miscarriage was defined as the interruption of pregnancy before the 20th week and perinatal mortality the fetal death from the 21st week of pregnancy until neonatal stage, occurring until the first week of life.

Statistical analysis was performed using simple frequency assessment of independent variables. Binary logistic regression was then used to assess the association between the dependent and independent variables, with respective odds ratio (OR), with $p \leq 0.05$ considered statistically significant using confidence intervals (CI) of 95%. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 21.0.

The study was approved by the Research Ethics Committee of the Paulista School of Nursing (CAAE 16395413.4.0000.5505) and planned in accordance with the resolution 466/2012 National Health Council.

RESULTS

A total of 183 pregnancies (representing 168 single and 15 twin fetuses) were registered, resulting in 198 potentially eligible cases; when the exclusion criteria was applied, all cases participated in the final analysis.

Maternal characteristics at the time of delivery included an average age of 30.03 ± 6.47 years (minimum, 18; maximum, >47 years), an average of previous pregnancies of 1.5 ± 1.2 (minimum, 0; maximum, 3), and an average gestational age at the time of abortion/birth of 37.84 ± 2.33 weeks (minimum, 12 weeks; maximum, 40 weeks), as shown in Table 1.

A total of 91.8% cases represented single-fetus pregnancies, of which 88.2% had fixed sexual partners, 25.3% were drug users, 74.4% had received prenatal care, 60.1% were aware of the diagnosis of HIV infection before pregnancy, 81.3% used antiretrovirals during pregnancy, and 73.2% had delivery by cesarean section, as shown in Table 2.

The prevalence of abortion and perinatal mortality was 6.1 and 4.0%, respectively.

The variables age, sexual partnership, serologically confirmed HIV-positive sexual partner, CD4+ T-cell count, viral load, presence of clinical complications, presence of co-infections, and hypertension were disproved as risk factors for miscarriage in pregnant HIV-infected women. The variables time of first prenatal consultation, preterm labor, labor type, use of antiretrovirals during childbirth, and undergoing a quick test for HIV before giving birth were not examined because these variables do not refer to data pertaining to preterm labor.

Binary logistic regression analysis identified the following risk factors for abortion: drug use, which raised this risk by 6.23 times (CI = 0.5 to 73.1); absence of participation in prenatal program, elevating the risk by 18.42 times (CI = 3.9 to 87.6); and multiple gestation, which raised the risk by 3.06 times (CI = 0.9 to 10.9) (Table 3).

The evaluation of the potential risk factors associated with perinatal mortality in HIV-infected pregnant women showed no association with the following variables: age, multiple gestation, sexual partnership, serological condition of the sexual partner, Director of prenatal, antenatal consultation, confirmation of HIV infection prior to or during pregnancy, CD4+ T-cell counts, viral load, presence of clinical complications, presence of associated infections, preterm labor, hypertension, and undergoing a rapid test for HIV before giving birth.

Table 1. Maternal characteristics.

Variables	Mean	Standard deviation	Minimum	Maximum
Age	30.03	6.47	18.00	47.00
Previous pregnancies	1.50	1.20	0.00	3.00
Gestational age at the time of the abortion/birth (weeks)	37.84	2.33	12.00	40.00

Table 2. Clinical characteristics of gestation.

Variables	n	%
Gestation (n = 183)		
single fetus	168	91.80
Multiple fetuses (twins)	15	8.20
Sexual partner (n = 85)		
Unique	75	88.2
Multiple	10	11.8
Injecting drug use (n = 75)		
Yes	19	25.3
No	56	74.7
Realization of pre-natal (n = 198)		
Yes	50	25.3
No	148	74.7
When we confirmed the diagnosis of HIV (n = 198)		
Before the pre-natal	119	60.1
In the pre-natal	54	27.3
at childbirth	23	11.6
At puerperium	2	1.01
Antiretroviral use during pregnancy (n = 198)		
Yes	161	81.3
No	37	18.7
Type of delivery (n = 198)		
Vaginal	53	26.8
Cesarean section	145	73.2

Risk factors for perinatal mortality included drug use (CI = 0.9 to 1.1); vaginal birth (CI = 1.2 to 26.1); and not taking antiretrovirals during childbirth (CI = 3.9 to 81.8), which increased the risk by 1.1, 5.6, and 17.7 times, respectively (Table 3).

DISCUSSION

In the present study, the prevalence of abortion and perinatal mortality associated with HIV-infected pregnant women and the risk factors associated with these conditions were studied.

The fertility rate of HIV-infected women is reduced by 55%, and infant mortality is 3 to 8 times greater for HIV-positive pregnant women compared with women not infected with HIV (Gray et al., 1998; Darak et al., 2011).

The prevalence of abortion (6.1%) was lower compared with that reported in other studies involving HIV-positive pregnant women (6.9 to 12.5%) (D'Ubaldo et al., 1998; Friedman et al., 2011), while the perinatal mortality (4.3%) was greater than that found in another study (1.7%) (Brocklehurst and French 1998).

Only illicit drug use was considered a risk factor for

Table 3. Risk factors associated with miscarriage and perinatal mortality.

Variables	Miscarriage				Perinatal mortality			
	OR	p*	IC		OR	p*	IC	
			Lower	Upper			Lower	Upper
Age – until 30 years (reference); 31 years or more.	4.1	0.4	1.1	15.7	2.2	0.2	0.5	9.9
Pregnancy – single fetus (reference); multiple fetus	3.1	**0.05**	0.9	10.9	0.8	0.9	0.1	7.1
Sexual partner - single (reference); multiple	1.1	0.3	1.0	1.1	1.1	0.2	1.0	1.1
HIV status of the sexual partner - not infected (reference); infected	7.2	0.7	0.8	60.4	1.9	0.4	0.4	10.7
Injecting drug use by pregnant women - no (reference); Yes	6.2	**0.01**	0.5	73.1	1.1	**0.001**	0.9	1.1
Realization of pre-natal - yes (reference); no	18.4	**0.001**	3.9	87.6	1.2	0.8	0.2	6.3
First prenatal visit - 1st and 2nd trimester (reference); 3nd trimester	-	-	-	-	3.1	0.4	0.1	52.9
Confirmation of HIV infection - before the prenatal (reference); prenatal / pregnancy	0.1	0.5	0.01	1.0	1.4	0.6	0.3	5.8
Viral Load Result - detectable; undetectable (reference)	2.7	0.3	0.3	25.4	2.8	0.3	0.3	25.4
Count of CD4 + T cells - until 350 (Reference); 351 or more	0.8	0.8	0.1	4.3	2.7	0.2	0.6	12.7
Presence of clinical complications - no (reference); Yes	0.2	0.1	0.1	1.5	1.2	0.7	0.3	5.5
Presence of associated infections - not (reference); yes	0.1	0.7	0.2	1.1	0.5	0.7	0.1	2.7
Preterm delivery - no (reference); yes	-	-	-	-	1.8	0.4	0.4	8.7
Hypertension - no (reference); yes	1.4	0.7	0.2	8.1	1.1	0.9	1.1	1.2
Type of delivery - vaginal; Cesarean (reference)	-	-	-	-	5.6	**0.02**	1.2	26.1
Antiretroviral use during labor - no; yes (reference)	-	-	-	-	17.7	**0.0001**	3.9	81.8
Conducting rapid HIV testing before delivery - yes (reference); no	-	-	-	-	1.3	0.8	0.1	11.9

***** Binary logistic regression testing.

both miscarriage and perinatal mortality. Furthermore, other studies have demonstrated an association between illicit drug use and an increased rate of abortion and perinatal mortality, particularly in those women who injected drugs, such as cocaine (Thackway et al., 1997; Forsyth et al., 2002; Barbosa et al., 2009). Another study showed that induced abortion is higher in HIV-negative women compared with that in HIV-positive women (Barbosa et al., 2009).

There is evidence that illicit drug use by pregnant women is associated with hepatitis, tuberculosis, and pre-eclampsia, which can increase the risk for spontaneous abortion by up to 3%, placental disorders and premature labor by up to 20%, in addition to clinical complications related to the use (Mayet et al., 2008; Joya et al., 2012; Izquierdo and Yonke, 2014).

Injectable illicit drugs cross the placenta and directly affect the fetus. This can occur at any stage of development. However, during the third trimester, fetal maternal blood flow and placental transport rates increased, contributing to the placental detachment; this is one of several factors causing the increasing number of premature births that increase morbidity and mortality. Moreover, a fetus exposed to illicit drugs may have a higher risk of presenting with birth defects, cardiovascular problems, compromised development and growth, prematurity, low birth weight, and death (Mayet et al., 2008; Yamaguchi et al., 2008; Joya et al., 2012; Izquierdo and Yonke, 2014).

Multiple gestation, illicit drug use, and not complying with prenatal programs were risk factors for abortion. It was verified that multiple gestation features a 3.6 times greater risk for the occurrence of miscarriages, corroborating data from another study that demonstrates that HIV infection in pregnant women increases the occurrence of premature births/abortions by up to 10 times (Ezechi et al., 2012).

The absence or low number of prenatal consultations is considered a risk factor for abortion independent of maternal serological

condition (Araújo and Tanaka, 2007; Geib et al., 2010; Konopka et al., 2010) and another study showed that 87.6% of pregnant women were diagnosed with HIV during prenatal care (Zimmermmann et al., 2011). In Brazil, it is recommended to participate in at least six prenatal consultations, regardless of the condition of maternal health, preferentially one in the first trimester, two in the second, and three in the third trimester of pregnancy as well as maintaining healthy habits (Paris et al., 2013; Martinelli et al., 2014; Pigatto et al., 2014). Prenatal consultation performed from the beginning of the pregnancy should be considered a protective factor for miscarriage in HIV-positive pregnant women.

Vaginal birth presented an increased risk of perinatal mortality 5.6 times higher than cesarean section, contradicting the findings of other studies that demonstrated a higher risk of perinatal/neonatal/infant death in children born naturally (Souza and Gotlieb, 1993; Maran and Uchimura, 2008). Studies have shown that delivery by elective cesarean section has a protective effect by decreasing the risk of perinatal mortality and by reducing brachial plexus injuries and bone fractures, and there is less exposure to HIV than during natural birth (Holmes and Hofmeyr, 2004; Molkenboer et al., 2004; Cardoso et al., 2010). However, there are no studies demonstrating the physiological relationship between vaginal delivery and perinatal mortality in HIV-infected pregnant women; these studies are limited to evaluating the rate of vertical transmission. Therefore, further studies are required in order to exclusively evaluate the physiological mechanisms that may explain the association observed in this study.

To the best of our knowledge, this study was the first to evaluate the absence of antiretroviral use during childbirth as an important risk factor for perinatal mortality, increasing the risk by 17.7 times. Other studies have shown that the use of antiretrovirals during pregnancy is a protective factor for premature deliveries by up to 5 times (Ezechi et al., 2012).

The limitations of this study are related to the fact that some data records were incomplete; however, the presented results may not be entirely inaccurate. It should be noted that the results obtained in this study are associated only with HIV-positive pregnant women, and data should not be extrapolated to healthy pregnant women or women with other co-morbidities. As well as shall be carefully evaluated the realization of preference of cesarean sections in relation to normal course of labor in order the scarcity of longitudinal similar studies in other populations to corroborate with the data observed in this research.

CONCLUSION

This study demonstrated that drug use, multiple gestation, and absence of prenatal consultations raise significantly the risk of abortion, and similarly, drug use, vaginal birth, and absence of antiretroviral use during childbirth elevate the risk of perinatal mortality. The implication for clinical practice and management of HIV-infected pregnant women should include performing actions aimed at eliminating the use of illicit drugs during pregnancy, enrollment in prenatal consultation programs from the beginning of pregnancy, a preference for elective cesarean section, and the use of antiretroviral drugs medications during childbirth in order for these actions to reduce the rates of abortion and perinatal mortality.

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