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Pregnancy outcomes and antiretroviral treatment in a national cohort of pregnant women with HIV: overall rates and differences according to nationality

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We used data from the main surveillance study of HIV and pregnancy in Italy to evaluate possible differences in pregnancy care and outcomes according to nationality. Among 960 women followed in 2001–06, 33.5% were of foreign nationality, mostly from African countries. Foreign women had lower rates of preconception counselling and planning of pregnancy. They had more frequently HIV diagnosed during pregnancy, with a later start of antiretroviral treatment and lower treatment rates at all trimesters but not when the entire pregnancy, including delivery, was considered. No differences were observed between the two groups in ultrasonography assessments, hospitalisations, AIDS

events, intrauterine or neonatal deaths, and mode and complications of delivery. Foreign women had a slightly lower occurrence of preterm delivery and infants with low birthweight. The results indicate good standards of care and low rates of adverse outcomes in pregnant women with HIV in Italy, irrespective of nationality. Specific interventions, however, are needed to increase the rates of counselling and HIV testing before pregnancy in foreign women.

Keywords Antiretroviral treatment, HIV, nationality, pregnancy.

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Introduction

Several studies have shown that the use of health services among pregnant women shows differences and disparities according to ethnicity or nationality. Such evidences include the following: among others, a higher probability of utilisation of mental health services among Caucasian women,¹ better prenatal care for white women delivering very low birthweight infants,² a lower use of periconceptional folic acid among nonwhite or non-Western women,^{3,4} and later start of

prenatal care among Hispanic women.⁵ Ethnicity of the mother has also been associated with differences in pregnancy outcomes, such as delivery of low birthweight infants,⁶ success of vaginal birth after caesarean delivery⁷ and morbidity for specific diseases during pregnancy.⁸

In the case of the pregnant women with HIV, timely and adequate prenatal care has additional and important implications because of the possibility of prevention of perinatal transmission to the newborn through antiretroviral (ARV) treatment, caesarean delivery and avoidance of breastfeeding.

A short duration of ARV treatment in pregnancy was observed for children who became infected despite maternal treatment in the European Collaborative Study,⁹ suggesting that a late start of care may be associated with transmission. Although low rates of mother-to-child transmission are currently reported from all the countries where preventive measures are undertaken, there is limited information about the quality of care and pregnancy outcomes in HIV-infected women of different nationalities living in such countries.

To provide information on this issue, we used data from the main surveillance study of HIV and pregnancy in Italy. Women of foreign nationality currently represent more than 30% of pregnant women with HIV in Italy,¹⁰ and we have previously shown that foreign nationality was an independent factor predicting a diagnosis of HIV infection during pregnancy.¹⁰ We here expand such observations analysing possible differences in some markers of prenatal care and in pregnancy outcomes, with the aim to explore whether women of foreign nationality are at risk of lower quality care during pregnancy, inadequate preventive measures against perinatal transmission, and worst pregnancy outcomes or complications.

Methods

We investigated possible differences in pregnancy outcomes according to nationality using data from the National Program on Surveillance on Antiretroviral Treatment in Pregnancy, a continuing national surveillance study established in Italy in 2001 to collect information on the safety and efficacy of ARV treatment in pregnancy. The study is observational, and the data collected reflect routine clinical care at each participating centre. Only HIV-positive pregnant women are included, and no indication is given for treatment of HIV infection or prophylaxis for mother-to-child transmission, which are defined by the treating physician. Informed consent is required for all enrolled women, using a patient information sheet that has received approval by the competent ethics committee. The study is coordinated by the Istituto Superiore di Sanità (ISS), the Italian National Institute of Health. Data are collected at 34 clinical centres by obstetricians, infectious diseases specialists and paediatricians, using specifically designed case report forms, and are then entered in a Microsoft-Access-based database at the Coordinating Centre at ISS, where queries are also generated and analyses performed. An advisory board and all participants are regularly updated with the results of the surveillance. All the results reported here are based on the data extracted on 10 October 2006 from the general database.

For the purpose of this analysis, we considered all HIV-positive women with a known nationality enrolled in our observational study between December 2001 (date of start of the study) and October 2006. For the women who had more than one pregnancy reported, only the first pregnancy

reported was considered. All pregnancies were included, irrespective of their completion with a delivery or early termination of pregnancy. In the analyses, the nationality of the women was dichotomised as Italian or non-Italian. Gestational age was determined on the basis of the last menstrual period (LMP), ultrasound biometry, or both. Preterm delivery was defined as delivery before 37 completed weeks of gestation. ARV treatment at conception was defined as continuing treatment at the date of LMP; the week of start of ARV treatment was calculated according to gestational age, assigning week 1 as week of start of ARV treatment to those women who were already on ARV treatment at LMP. Information and measurements during pregnancy were collected at routine visits performed in the three trimesters of pregnancy, with no restrictions in gestational age at entry into prenatal care.

Quantitative variables were compared using the *t* test for independent samples or the Mann-Whitney *U* test, according to the characteristics of the distribution (symmetrical or skewed, respectively), and categorical variables were compared using Pearson χ^2 test. All the analyses were performed using the SPSS software, version 13.0.1, 2004 (SPSS Inc., Chicago, IL, USA).

Results

At the date of data extraction, 960 women had available information for the analysis. One-third of the women (322/960, 33.5%) were of foreign nationality, belonging to 63 different countries, mostly from Africa (Table S1). The general characteristics of the entire group and of women with Italian nationality and with foreign nationality are reported in Table S2. When the women with Italian nationality and those with foreign nationality were compared, the results showed some significant differences between the two groups. Foreign women were younger, less likely to have a history of intravenous drug use and hepatitis C virus (HCV) infection, and also less likely to have indication to ARV treatment for their own health. Compared with Italian women, they were also more frequently antiretroviral naive and more likely to have a current partner with unknown HIV status. In terms of preconception care, they were less likely to have received preconception counselling (here defined broadly as advice on multiple health issues regarding pregnancy, including HIV) (14.5 versus 35.4%, $P < 0.001$), to have planned current pregnancy (27.2 versus 42.3%, $P < 0.001$), and to be aware of being HIV-infected before pregnancy (52.1 versus 87.6%, $P < 0.001$).

No differences were found between the two groups in clinical severity of HIV disease (proportion of women with an AIDS diagnosis at the beginning of pregnancy) and obstetric/gynaecological history (sexually transmitted diseases, gravidity, voluntary pregnancy terminations, miscarriages and past preterm deliveries).

Women of foreign nationality started ARV treatment significantly later during pregnancy (week 14, compared with week 7,

$P < 0.001$) and were slightly but significantly less likely at all trimesters to be on ARV treatment, compared with women of Italian nationality (Table 1). However, when only the pregnancies lasting more than 24 weeks were considered, no differences were found in the proportion of women who received ARV treatment at anytime during pregnancy, including during delivery (97.6 and 97.5% in the two groups, respectively), and in the proportion of women who received intravenous zidovudine at delivery (92.8% in both groups). The CD4 count and viral load values in the third trimester were also similar between the two groups, with no differences observed in the proportions of women with less than 1000 and less than 50 copies/ml of plasma HIV RNA in the third trimester. There were no differences in

the proportion of women who underwent ultrasonography during visits at different trimesters (Table 1).

In terms of morbidity during pregnancy and of pregnancy outcomes, no differences between the two groups were observed in the rates of hospitalisations, AIDS events during pregnancy, intrauterine or neonatal death, elective caesarean section, or complications of delivery; newborn data showed a slightly higher gestational age at delivery in foreign women, which translated into a significantly higher weight of the newborns and into a significantly lower occurrence of preterm delivery and low birthweight (Table 1). The vast majority (95%) of newborns received HIV prophylaxis against vertical transmission, usually represented by oral zidovudine for

Table 1. ARV treatment, evaluations during pregnancy and pregnancy outcomes

	Total	Italian nationality	Foreign nationality	P value
Week of gestation of first ARV treatment in current pregnancy,* mean (range); n = 781	10.1 (1–41)	7.8 (1–41)	14.9 (1–41)	<0.001
On ARV treatment (%)				
First trimester, n = 550	43.3	46.0	35.6	0.029
Second trimester, n = 590	80.7	85.6	70.6	<0.001
Third trimester, n = 602	92.0	93.9	88.3	0.016
Any ARV treatment during pregnancy, n = 610**	97.5% (595/610)	97.5% (391/401)	97.6% (204/209)	0.939
Use of intravenous zidovudine at delivery, n = 595	92.8% (552/595)	92.8% (360/388)	92.8% (192/207)	0.989
Ultrasonography performed at visits (%)				
First trimester, n = 546	89.4	91.0	85.4	0.057
Second trimester, n = 565	97.3	97.9	96.3	0.279
Third trimester, n = 562	98.2	98.6	97.5	0.337
CD4 cell count at third trimester (cells/mm³), mean (range); n = 533	495 (10–1867)	502 (21–1584)	481 (10–1867)	0.549
HIV RNA at third trimester (copies/ml), median (IQR); n = 515	60 (50–453)	68 (50–417)	50 (50–660)	0.286
HIV RNA at third trimester (%), n = 515				
<1000 copies/ml	79.2	79.5	78.7	0.816
<50 copies/ml	48.5	46.3	52.8	0.159
Women with hospitalisation (%)				
At first trimester, n = 554	4.2	4.3	3.8	0.807
At second trimester, n = 598	9.0	7.5	11.8	0.076
At third trimester, n = 603	17.7	17.0	17.7	0.526
Any AIDS event during pregnancy (n = 695)	0.3% (2/695)	0.2% (1/445)	0.4% (1/249)	0.676
Intrauterine (>22 weeks) or neonatal death, n = 633	1.4% (9/633)	1.2% (5/417)	1.9% (4/216)	0.511
Elective caesarean delivery, n = 613	79.9% (490/613)	79.4% (320/403)	81.0% (170/210)	0.650
Gestational age at delivery (weeks), mean (range); n = 616	36.7 (25–41)	36.6 (25–41)	37.1 (30–41)	0.002
Preterm delivery (<37 weeks), n = 616	26.9% (166/616)	29.6% (120/405)	21.8% (46/211)	0.038
Weight of the newborn (g), median (IQR); n = 580***	2850 (2530–3107)	2800 (2460–3070)	2900 (2630–3200)	0.001
Low birthweight (<2500 g), n = 580	23.1% (134/580)	27.2% (103/379)	15.4% (31/201)	0.001
Complications of delivery, n = 590	8.1% (48/590)	6.7% (26/389)	10.9% (22/201)	0.073
HIV prophylaxis in the newborn, n = 540	95.0% (513/540)	95.1% (327/344)	94.9% (186/196)	0.935

IQR, interquartile range.

*Week 1 assigned to those women who were already on treatment at LMP.

**Only the pregnancies with more than 24 weeks of gestation were considered.

***Only liveborn from singleton pregnancies considered.

6 weeks, with no differences between the two groups (95.1 versus 94.9%, $P = 0.935$). No differences were observed for all the outcomes listed in Table 1 between African and non-African women within the group of foreign women (data not shown).

Seven cases of transmission were observed (transmission rate: 1.9%, based on 370 children with adequate follow up). Five of them were in Italian women and two in women of foreign origin. The two cases in foreign women include one woman who did not receive ARV treatment at all during pregnancy because of HIV diagnosed after delivery and one woman who was diagnosed at delivery and was administered only intrapartum treatment. The five cases in Italian women included four women who had received ARV treatment during pregnancy and one woman who received intrapartum treatment only. Given the small numbers of cases, no test was applied to evaluate the significance of the rate difference between the two groups or the presence of possible factors predicting transmission.

The main differences observed between the two groups were a later start of ARV treatment and lower rates of ARV treatment in each trimester among foreign women. These women also had higher gestational age at delivery, lower occurrence of preterm delivery and higher weight at birth for the newborn. Overall, all these findings could be at least partly related to the significantly higher occurrence of an HIV diagnosis during pregnancy observed in foreign women.

To define the role of nationality in the differences observed independently from the occurrence of an HIV diagnosis during pregnancy, we performed a subanalysis in which only the women with HIV infection already known before pregnancy were considered. The results showed for most of the comparisons the absence of significant differences between Italian and foreign women: the two groups had similar proportions of antiretroviral-naïve women (19.0 versus 24.5%, $P = 0.148$), women with indication to ARV treatment for their own health (80.7 versus 75.4%, $P = 0.183$), and women on ARV treatment at each trimester (50.6 versus 48.0% at first trimester, $P = 0.649$; 89.4 versus 83.2% at second trimester, $P = 0.086$; 95.8 versus 96.1% at third trimester, $P = 0.896$). Furthermore, no differences were observed in the rates of hospitalisations, ultrasonography, overall treatment during pregnancy, use of intravenous zidovudine at delivery, CD4 counts and viral load levels in the third trimester (data not shown).

Nonetheless, the subanalysis confirmed a later start of ARV treatment in foreign women (week of gestational age: 5.9 versus 8.6, $P = 0.001$) and a higher occurrence of low birth-weight infants (<2500 g) among Italian women (28.9 versus 16.8%, $P = 0.020$), with differences at the threshold of statistical significance for gestational age at delivery (36.5 versus 36.9 weeks, in Italian and foreign women, respectively, $P = 0.055$), preterm delivery (32.5 versus 23.6%, $P = 0.081$), and infant weight at birth (2722 versus 2843 g, $P = 0.050$).

Discussion

Our study examined different aspects of treatment and care during pregnancy and provided information on ARV treatment and pregnancy outcomes in a large cohort of HIV-infected women of different provenance followed in a European country. Recent data on HIV seroprevalence at delivery in Italy indicate an estimated seroprevalence of 0.66 per 1000, corresponding to an estimate of 346 liveborns from HIV-positive mothers in 2002.¹¹ Our study and the data provided here, based on about 1000 pregnancies reported in less than 5 years, represent the vast majority of the pregnancies occurring in HIV-positive women in Italy, with a nationwide distribution of participating centres.

Foreign women had some distinct demographic characteristics, represented by younger age, less frequent history of intravenous drug use, and lower rates of HCV co-infection. In terms of preconception care, we observed for these women significantly lower rates of preconception counselling, planning of pregnancy, and HIV diagnosis before conception. These findings indicate the need of interventions aimed at improving the access of foreign women to HIV testing and preconception counselling services. The potential benefits of preconception care are well known and include identification of risk factors for adverse maternal outcomes, treatment or stabilisation of existing medical conditions, and provision of information and education.¹² Women who acquire knowledge of being HIV infected before pregnancy might decide not to get pregnant or to postpone pregnancy, and those who already know to be HIV infected could be better managed and properly informed about several issues concerning HIV, pregnancy, ARV treatment, adherence, adverse effects and HIV transmission. Such interventions are likely to reduce the main disparities observed in our study, represented by a later start of ARV treatment and by a lower proportion of women of foreign origin on ARV treatment at each trimester.

It is important to note, however, that such differences, which also might reflect a less frequent indication to ARV treatment for their own health, did not negatively affect pregnancy outcomes, and no differences were observed in the main outcomes studied, represented by AIDS events, hospitalisations, mode of delivery, delivery complications, and intrauterine death. In addition, no differences based on nationality were observed in other markers of care received, such as ultrasonographic evaluations, CD4 counts, and viral suppression at the end of pregnancy. It is possible, given the role of ARV treatment on preterm delivery, that the later start of treatment may have partly protected foreign women against the occurrence of preterm delivery, resulting in a small but significant increase in duration of pregnancy and weight of the newborn.

Overall, the findings on the entire cohort indicate not only similar levels of pregnancy care among women of Italian

nationality and women from foreign countries but also good standards of care and treatment at a national level. The vast majority of the women and newborns received full preventive care against HIV transmission: only 2.5% of the women did not receive antiretroviral therapy in pregnancy, and more than 90% received intravenous zidovudine at delivery. The observed 80% rate of elective caesarean delivery is also quite positive, being higher than the 61% rate reported in the European Collaborative study⁹ and substantially identical to that reported by Navè *et al.*¹³ in Sweden in recent years. The figure for newborn prophylaxis is also favourable, with a 95% coverage among the newborns of the cohort. Other positive findings include the very low rate of AIDS events during pregnancy and the low rates of complications of delivery. Our data confirm the increasing frequency of preterm delivery, which occurred in about one-quarter of the women, matching the findings of the European Collaborative Study.⁹

In summary, our study shows overall good standards of care and low rates for adverse outcomes in pregnant women with HIV in Italy, irrespective of nationality. Foreign women, however, were less likely to receive counselling and HIV testing before pregnancy and started ARV treatment significantly later during pregnancy. Specific interventions to eliminate these differences may be beneficial in several aspects. The only two cases of HIV transmission currently reported among foreign women in our study were actually because of a late or missed HIV diagnosis during pregnancy, and it is likely that a timely start of care might have prevented such occurrence.

The general scenario that we describe, characterised by a relevant proportion of foreign women among pregnant women with HIV in a context of general low HIV prevalence and adequate resources, is also applicable to other Western countries. The new data that we produced may be useful to healthcare providers of other countries to ascertain the possible presence of similar differences in their countries, define specific interventions directed to foreign women, and eventually to improve the efficiency of counselling and preconception care services.

Supplementary material

The following supplementary materials are available for this article:

Table S1. Provenance of the women of foreign nationality.

Table S2. General characteristics at conception.

Appendix S1. The Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy.

These materials are available as part of the online article from: <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1471-0528.2007.01355.x>.

(This link will take you to the article abstract).

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