RESEARCH LETTER

Good prenatal detection rate of major birth defects in HIV-infected pregnant women in Italy

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Available evidence indicates no major increase in the risk of birth defects for the offspring of HIV-infected women who receive antiretroviral treatment in pregnancy.[1–4] There is, however, no information on the extent to which such defects are diagnosed prenatally. Women with HIV need a regular monitoring of several specific conditions, such as antiretroviral treatment, comorbidities, co-infections, and possible immunodeficiency that should translate into a proactive follow-up during pregnancy, with an expected high rate of antenatal detection of birth defects. However, they might also be at risk of infrequent access to health services that may lead to missed antenatal visits and limited prenatal testing. In order to investigate this issue, we evaluated the rate of prenatal diagnosis of major defects within the National Program on Surveillance on Antiretroviral Treatment in Pregnancy, the largest cohort of HIV-infected pregnant women in Italy.[5] In this study, information on possible presence of defects is requested for all live births and in the case of miscarriage, stillbirth, and pregnancy termination. Major birth defects were defined according to the Antiretroviral Pregnancy Registry definition[6] and grouped as chromosomal anomalies or major structural defects. Major structural defects were further classified as severe or non-severe, considering as severe all the structural defects listed in the EUROCAT survey by Garne *et al.*,[7] all the critical congenital heart defects listed by Peterson *et al.*,[8] and other less common defects according to expert opinion (PM). Quantitative variables were compared by the *t*-test and categorical data by the chi-square test, with odds ratios (OR) and 95% confidence intervals (CI) calculated. Temporal trends in rate of detection of antenatal defects and in rate of elective termination of pregnancy were analyzed by the chi-square test for trend. *P*-values <0.05 were considered significant. All statistical analyses were defined following the data extraction from the database and were performed with the SPSS software, version 22 (IBM, Somers, NY, USA).

As of 27 February 2015, 2162 pregnancies (2202 cases: 289 no live births, 1833 live singletons, 74 live births from twin pregnancies, and 6 from triple pregnancies) had available information on pregnancy outcome and on presence of birth defects. Among them, 93 major defects (chromosomal: 21; structural: 72) were identified, for an overall prevalence of 4.2% [95%CI 3.4, 5.1%] and a prevalence among live births of 3.5% [95%CI 2.7, 4.3]. Mean maternal age was not significantly different between cases with no defects (32.2 years) and with structural defects (32.1 years) ($p=0.890$) but was significantly higher for cases with chromosomal anomalies (36.3 years) compared with the other two groups (cases with no defects and cases with structural defects, $p<0.001$ for both comparisons).

Overall, 51.6% (48/93) of defects were diagnosed before birth. Their complete list is reported in Table 1. Following antenatal detection, 2 cases ended in miscarriage (4%), 19 (40%) in elective termination of pregnancy, 4 (8%) in late (>22 weeks) intrauterine fetal death, and 23 (48%) in live births. The rate of elective termination of pregnancy following antenatal detection of major defects showed no changes between 2001 and 2014 (2001–2005: 40.0%; 2006–2009: 42.9%, 2010–2014: 41.3, $p = 0.912$, chi square for trend) but showed significant differences by category of defect, with chromosomal defects more likely to lead to elective

Table 1 **List of major birth defects observed: diagnosed antenatally**

Defect classification by organ system (*n*)	Defect (*n*)	Test (*n*)	Pregnancy outcome (*n*)	Maternal age (years)
Chromosomal (*n*: 14)	Trisomy XXX (1)	Amniocentesis	Live birth	Unknown
	Trisomy 21 (6)	Ultrasound (3) Amniocentesis (3)	Stillbirth (1) ETOPFA (5)	43, 36, 42, 41, 35, 41
	Trisomy 18 (5)	Amniocentesis (3) CVS (1) Ultrasound (1)	ETOPFA (5)	34, 33, 35, 42, 37
	Turner Syndrome (45, X) (1)	Ultrasound, karyotype	ETOPFA	35
	Mosaic trisomy 8 with structural abnormalities (1)	Ultrasound, karyotype	ETOPFA	30
Obstructive heart defects, left-sided (1)	**Hypoplasia/agenesis of left ventricle (1)**	Ultrasound	ETOPFA	34
Obstructive heart defects, right sided (2)	**Hypoplasia of right heart and pulmonary artery (1)** Pulmonary valve stenosis (1)	Ultrasound Ultrasound	Live birth Live birth	22 35
Conotruncal heart defect (1)	**Fallot tetralogy (1)**	Ultrasound	Live birth	24
Other heart defects (5):	Right-sided aortic arch (1) Ventricular septal defect (2) Dilated Galen vein, cardiomegaly (1) Ventricular and atrial septal defect (1)	Ultrasound (5)	Live birth (4) Stillbirth (1)	29, 32, 27, 32, 42
Other circulatory system (1)	Patent ductus arteriosus (ga > 36 weeks) (1)	Ultrasound	Live birth	34
Muscoloskeletal (5)	Bilateral club foot (3)	Ultrasound (3)	Live birth	33, 27, 39
	Osteogenesis imperfecta (1)	Ultrasound	Live birth	26
	Conjoined twins (1)	Ultrasound	ETOPFA	29
Male genitalia (1)	Hypospadia (1)	Ultrasound	Live birth	39
Central nervous system (6)	**Arnold-Chiari syndrome (1)** **Hydrocephalus with hypoplasia of corpus callosum (1)** Cerebral igroma (1) **Triventricular hydrocephalus (1)** **Tetraventricular hydrocephalus with large schisis in cerebellar vermis (1)** Bilateral choroid plexus cysts (1)	Ultrasound (6)	Stillbirth (2) Live birth (1) Miscarriage (1) ETOPFA (2)	37, 37, 37, 30, 24, 39
Renal and urinary system (3)	Unilateral agenesis of kidney (1) Ectopic (pelvic) kidney (1) Bilateral kidney hypoplasy (1)	Ultrasound (3)	Live birth (3)	33, 34, 28
Upper gastrointestinal system (2)	**Gastroschisis (2)**	Ultrasound (2)	Live birth (2)	25, 31
Face and neck (2)	Cystic hygroma of the neck (1) Labiopalatoschisis (1)	Ultrasound (2)	ETOPFA (1) Live birth (1)	28, 33
Limb reduction defects (1)	**Left arm hypodysplasia, right forearm agenesis, right hand hypoplasia (1)**	Ultrasound	ETOPFA	32
Multiple systems affected (4)	Hypoplasia of corpus callosum, atrial septal defect (1) Severe hydrops foetalis, intestinal abnormalities (1) Ambiguous genitalia, duodenal atresia, imperforate anus (1) Cardiac abnormalities, cystic hygroma (1)	Ultrasound (4)	Live birth (2) Miscarriage (1) ETOPFA (1)	29, 42, 36, 31

ETOPFA, elective termination of pregnancy for fetal anomaly; ga, gestational age; CVS, chorionic villus sampling. Severe structural defects are reported in bold.

termination of pregnancy compared with structural defects (OR: 21.4 [95%CI 3.9, 119.1, $p < 0.001$).

The antenatal detection of defects was not influenced by nationality of the women (rates of detection: 64.4% and 50.0% among foreign and Italian women, respectively, OR 1.81 [95% CI 0.79, 4.17], $p = 0.161$) or by timing of first presentation in pregnancy (mean week of first maternal visit in pregnancy: 10.2 and 10.9 in cases with and without antenatal detection, respectively, $p = 0.474$). The rate of detection was 60.0% among women who were on antiretroviral treatment at conception and 41.2% among women not on antiretroviral treatment at conception (OR 2.14 [95%CI 0.90, 5.12], $p = 0.086$). Being on antiretroviral therapy (ARV) at conception was not associated with a higher prevalence of defects ($p = 0.083$) or with higher severity of defects in this group (odds ratio for severe vs. non- severe structural defects by ARV status at conception: 0.958 [95%CI 0.293, 3.139], $p = 0.944$).

The rate of antenatal detection was 42.6% in 2001–2005, 57.7% in 2006–2009, and 65.0% in 2010–2014 ($p = 0.073$, chi square for trend). Detection rates by category of defect

Table 2 List of major birth defects observed: not diagnosed before birth

Defect classification by organ system (*n*)	Defect (*n*)	Pregnancy week of first visit	Ultrasonography at 2nd trimester	Maternal age (years)
Chromosomal (7)	Trisomy 21 (6)	7,9,10,12,21, unknown	Yes (4), unknown (2)	29,33,37,38, 39,42
	Trisomy 22 (1)	8	Unknown	37
Conotruncal heart defects (1)	**Transposition of great vessels (1, deceased after birth)**	16	Yes	32
Obstructive heart defects, right sided (2)	Pulmonary stenosis, atrial septal defect and ductus arteriosus (1)	21	Yes	27
	Pulmonary valve stenosis (1)	9	Yes	43
Other heart defects (8):	Atrial septal defect (6; ga > 36 weeks)	8,12,13,2, unknown (2)	Yes (3), unknown (3)	29,31, 32,33,33,39
	Ventricular septal defect (2, ga > 36 weeks)	6, unknown	Yes, unknown	32,43
Other circulatory system (1)	Patent ductus arteriosus (ga > 36 weeks) (1)	2	Yes	38
Muscoloskeletal (7)	Bilateral club foot (1)	11	yes	39
	Floating thumb (1)	10	yes	33
	Hip development abnormality (hip immaturity) (1)	12	Yes	36
	Hip dysplasia (1)	10	Yes	30
	Microcephaly (1)	unknown	Unknown	37
	Inguinal hernia with/without undescended testicle (2)	8, 11	Yes (2)	39,37
Male genitalia (6)	Undescended testicle (4; ga >36 weeks or surgery)	7, 9,10,14	Yes (3), unknown	23,25,32,37
	Hypospadia (2)	3,13	Yes (2)	23,30
Central nervous system (2)	**Hydrocephalus, hypoplasia of corpus callosum (1)**	8	Yes	38
	Syringomyelia (1)	Unknown	Unknown	31
Renal and urinary system (4)	Unilateral multicystic kidney (1)	19	Unknown	24
	Unilateral agenesis of kidney (1)	21	Yes	29
	Stenosis of renoureteral junction (1)	5	Yes	33
	Unilateral kidney hypodysplasia (1)	12	Yes	34
Upper gastrointestinal system (1)	Pyloric stenosis (1)	12	Yes	19
Face and Neck (2)	Microphtalmia (1)	9	Yes	30
	Congenital muscular torticollis (1)	12	No	32
Limb addiction defects (2)	Polydactyly (hand) (2)	7, 8	Yes (2)	32,39
Multiple systems affected (2)	Ventricular septal defect, pyloric stenosis, umbilical hernia (1)	10	Yes	22
	Pectus excavatum, atrial septal defect (1)	8	Yes	26

ga, gestational age. Severe structural defects are reported in bold.

were 66.7% for chromosomal abnormalities (14/21) and 47.2% (34/72) for structural defects (OR: 2.23, [95%CI 0.81, 6.19], $p = 0.122$).

Fourteen structural defects (highlighted in bold in the Tables) were classified as severe according to the definition criteria. Twelve of them were detected during pregnancy, for a prenatal detection rate of 85%.

All the cases with major defects diagnosed only after birth are reported in Table 2. They include 7 cases with chromosomal anomalies, 36 cases with non-severe structural defects, and 2 with severe structural defects (transposition of great vessels and hydrocephalus). None of the seven women with missed antenatal diagnoses of chromosomal abnormalities had undergone prenatal genetic testing in pregnancy (including non-invasive screening tests such as biochemical markers or nuchal translucency), although most of them had indication and opportunity to be tested (age ≥ 37 years: 5/7; first visit in pregnancy before 14 weeks: 5/7; at least one ultrasonography scan performed during pregnancy: 4/7). Similarly, the majority of the women with missed antenatal diagnoses of structural defects had adequate access to antenatal care and diagnostics, as indicated by the proportion of women who had a first visit in pregnancy before 25 weeks (86.8%) or an ultrasound scan during second trimester (76.3%).

In this study, we analyzed for the first time the rate and determinants of antenatal diagnosis of major birth defects among women with HIV, showing that roughly half of these defects were not diagnosed before birth. The rate of detection was higher for chromosomal anomalies, but one-third of such defects were not diagnosed during pregnancy, even in the presence of timed antenatal visits and indication to testing because of advanced maternal age. We are unfortunately unable to define the reasons of these missed diagnoses, but HIV status may influence prenatal genetic diagnosis choices.[9] Further studies will have to address to which extent procedures for prenatal diagnosis of chromosomal abnormalities are offered to women with HIV and to which extent and why they are refused. Potential vertical HIV transmission as a consequence of invasive procedures such as amniocentesis and villocentesis should not represent a concern, because available evidence indicates no additional risk of transmission when such procedures are performed under antiretroviral treatment and in a background of suppressed maternal viral load.[10]

When major defects were diagnosed prenatally, elective pregnancy termination was common (40%). This outcome involved (with the only exception of a case of a live birth with trisomy X and a case of trisomy 21 ending in intrauterine death) all prenatal diagnoses of chromosomal anomalies. Elective termination of pregnancy was less common in the presence of prenatally diagnosed structural defects. This indicates a strong difference in decision-making, most likely based on the level of expected disability and assistance needed, and on the possibility to revert through surgical correction a significant proportion of structural defects. In terms of predictors of prenatal diagnosis, the rate of antenatal detection was not affected by origin of the women (which may be linked to differences in access to care) or week of first visit in pregnancy. Although our data do not show a significantly higher detection rate among women on antiretroviral treatment at conception, this condition may facilitate a regular link to care throughout pregnancy and increase the number of women eligible for the invasive procedures that require undetectable maternal viral load.[10] Compared with the general population, the rate of prenatal detection for structural defects that we observed in women with HIV (47.2%) is consistent with data from a European survey based on population registries and conducted between 1995 and 1999, which showed for a selected list of severe defects a detection rate of 64% across Europe (range 25–88%), with rates in the two Italian participating centers of 50% and 58%.[7] Actually, when we considered only severe structural defects, using a modified version of the aforementioned classification, the antenatal detection rate was very high, with more than 80% of severe structural defects diagnosed before birth. This indicates a good prenatal diagnosis of screening-detectable congenital defects in women with HIV, suggesting at least similar prenatal detection rates compared with the general population. Moreover, our finding of effective prenatal diagnosis among mothers of foreign origin is reassuring in terms of equality of access to diagnosis and care. Similarly reassuring is the finding that among pregnant women with HIV, missed prenatal diagnosis of major birth defects was not due to late presentation during pregnancy or lack of access to antenatal care and mostly involved, among structural defects, those of lesser severity. In order to obtain further improvement, future studies will have to explore the aspects of communication between pregnant women with HIV and their care providers, with particular reference to prenatal diagnosis of chromosomal disorders, investigating and defining the determinants that influence decision-making on prenatal diagnosis and pregnancy continuation.

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Ethics approval

The ethics approval was obtained on 28 September 2001 from the Ethics Committee of the I.N.M.I. Lazzaro Spallanzani in Rome (ref. deliberation n. 578).

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Exposure to antiretroviral treatment in pregnancy does not seem to increase the risk of birth defects, but there is no information on the rate of prenatal detection of such defects.

WHAT DOES THIS STUDY ADDS?

- We provide for the first time, in a national case series, information about prenatal detection rate in women with HIV (51.6% for any major defect, 66.7% for chromosomal abnormalities, and 85% for severe structural defects).

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APPENDIX 1. THE ITALIAN GROUP ON SURVEILLANCE ON ANTIRETROVIRAL TREATMENT IN PREGNANCY

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