Prevalence of colpocytological abnormalities in pregnant HIV-positive women and risk factors

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BACKGROUND: Coinfection with Human Papillomavirus (HPV) and Human Immunodeficiency Virus (HIV) in pregnant women is a growing problem, posing a high risk of complications and oncologic progression.

PATIENTS AND METHODS: Between January 2010 and December 2016 we enrolled all HIV positive pregnant women referred to our High Risk Pregnancy Center and as controls all HIV negative pregnant women referred to our Colposcopy and Cytology Centre. We performed Pap-test and colposcopy in all patients to evaluate the prevalence of colpocytological abnormalities in each group. One year after delivery, we repeated Pap-tests in all women to assess any evolution of the primary lesions. We also checked for any link between cytological lesions and some features in HIV-positive patients.

RESULTS: In the HIV-positive group the Pap-test was normal in 49 patients (75%), while the colposcopic examination was normal in 42 women (64%). In the control group, the Pap-test was negative in 113 cases (95%), and the colposcopic examination was normal in 112 patients (93%). One year after delivery the Pap-test showed a regression of cytological lesions in both groups, but was statistically significantly higher in HIV-positive women. Finally, HIV-positive women showed a higher prevalence of colpocytological abnormalities, depending on nationality, partner HIV-concordance, CD+ T-cell count and viral load.

CONCLUSION: Our results confirm that HIV-positive pregnant women are an "at risk population" for cervical abnormalities, identifying pregnancy as the best moment to sensitize women about the importance of screening for cervical cancer. Moreover, some features identify subgroups with an increased risk, requiring close follow-up and personalized management.

Key Words: *Human Immunodeficiency Virus; Pregnancy; Colpocytological abnormalities; Follow-up; Risk factors*

HIV infection is an increasingly widespread disease, with a growing number of infected women and related gynaecologic manifestations. Meanwhile, the treatment of opportunistic infections and active antiretroviral therapy (HAART) has greatly improved patients' survival and quality of life. This is closely linked with a rising desire for pregnancy (1).

Human papillomavirus (HPV) can complicate the pregnancy; this DNA-virus is associated with epithelial hyperplasia and cervical cancer; each genotype has different oncogenic properties, and two groups are generally recognized: low-risk and high-risk HPV (LR-HPV and HR-HPV, respectively). Seven among the HR-HPV group: 16, 18, 31, 33, 45, 52, 58 are related to nearly 90% of all cervical cancers in the general population; in particular, HPV16 and 18 account for 70% of all cases (2).

HPV infection is endemic: in literature 26-46% of sexually active women under the age of 25 are estimated to be infected. Generally, the infection is persistent and without clinical evidence of disease but some factors can induce virus activation and development of the pathological process (3).

These include:

- Acquired or genetically immunodeficiency
- Pregnancy or other situations changing the immune response
- Lower genital tract inflammatory disease (inflammation promotes basal cells infection)
- Steroids
- Co-infection with Herpes simplex genital virus (HSV-2)
- Smoking
- Diabetes mellitus (4)

During pregnancy there is an increased prevalence of HPV infection and a faster progression from squamous intraepithelial lesion to carcinoma, even in healthy women, probably due to an impaired immune response associated to pregnancy itself (5).

Immuno-depression caused by chronic HIV infection, added to this paraphysiological state, enhances HPV pathogenicity. HIV and HPV coinfection have a synergistic effect: Tat HIV protein is able to increase expression of HPV oncoproteins (E6/E7); this is why HIV positive patients have a five-fold greater risk of Cervical Intraepithelial Neoplasia (CIN).

Finally, HIV infection results associated with: an increased prevalence of HPV infections (at least twice) and related complications; recurrent diagnoses of rare, new or high-risk viral types; multiple infections; lower spontaneous resolution.

Linkage with HIV immune-depression is confirmed by the higher prevalence of all these complications in patients with a lower T-cell CD4+ count (6).

The present case-control study compared a group of HIV-positive pregnant patients with a group of HIV-negative pregnant women: all patients were interviewed to obtain detailed clinical and socio-demographic data, diagnostic tests were subsequently performed to evaluate the prevalence of colpocytological lesions in each patient.

Previous studies have assessed the higher prevalence of lesions in HIV-positive pregnant women and correlations with some socio-demographic and clinical-laboratory features (1). The aim of this study was to explore these assessments and especially to recognize, in HIV-positive pregnant women, any new demographic, clinical or laboratory element predictive of the development of colpocytological lesions, thus identifying useful risk factors never explored before, to detect pregnant women with a higher risk of HPV complications. This would allow personalized screening and follow-up to be activated.

PATIENTS AND METHODS

This study enrolled all consecutive HIV-positive pregnant women referred,

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2006

from January 2010 to December 2016, to the High Risk Pregnancy Center in the II UO of Gynaecology and Obstetrics, University Hospital of Bari, Italy. In the same period, all HIV-negative pregnant women referred to the Colposcopy and Cytology Center of the same unit were enrolled in the control group.

A detailed clinical history provided all necessary information about: socio-demographic data (age, race, educational level, parity, marital status, menarche, age at first coitus, use of contraceptive methods, mode of HIV acquisition, number of sexual partners, current and past smoking status, toxic dependence, infectious state of partner, history of sexually transmitted infections), clinical and laboratory data (kind and start of antiretroviral therapy in regard to the pregnancy dates, disease stage according to the CDC classification, CD4+ T-cell count, HIV viral load, co-infections) (Tables 1 and 2).

The CDC classification evaluates the progressive impairment of cell-mediated immunity and its relation with the onset of opportunistic infections and specific cancers. As known, major opportunistic infections denote the evolution of HIV to AIDS (7).

CDC categorization is based on:

- **Clinical data:**

  A = asymptomatic/acute HIV/persistent generalized lymphadenopathy

  B = symptomatic conditions, not A or C

  C = AIDS-indicator conditions

- **CD4 T-cell count:**

  1. ≥ 500 cells/μL
  2. 200-499 cells/μL
  3. <200 cells/μL

Patients in categories A3, B3 and C1-C3 are considered to have AIDS. Both HIV positive and negative pregnant women underwent cytological exo- and endo-cervical screening at the time of their first access to our center. Pap-tests were performed according to common standards (Ayre spatula and Cytobrush) and cytological alterations were classified as negative or positive: ASCUS, AGC, ASCH, L-SIL, H-SIL, conforming to the Bethesda System (Table 2).

Colposcopic examination, assessed with the IFCPC international classification criteria, was performed in all patients; colposcopic findings were classified as negative (grade 0/normal transformation zone) or positive (grade 1/abnormal transformation zone with minor abnormalities and grade 2/abnormal transformation zone with major abnormalities) (8) (Table 2).

The kind of antiretroviral therapy and if the patient had started therapy before or during pregnancy were also assessed. Currently, HIV infection is treated with "highly active antiretroviral therapy" (HAART), a combination of anti-HIV drugs that can reduce mortality in these patients. These drugs belong to different categories: entry inhibitors, fusion inhibitors, reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, multi-class combination products. Healthcare providers recommend that people infected with HIV take a combination of antiretroviral drugs (the approach called HAART) to prevent the HIV strains from becoming resistant to one type of antiretroviral drug. Obviously, strict adherence to treatment is necessary.

One year after delivery, the Pap-test was performed again in all patients: cases of H-SIL persistence were treated by conisation, progression towards carcinoma of uterine cervix required radical hysterectomy. Exclusion criteria were denial of consent and patients with incomplete clinical history or clinical data.

HIV pregnant women were enrolled and managed according to the 'Italian National Program on Surveillance of Antiretroviral Treatment in Pregnancy', an observational study started in Italy in 2001, and including our centre. The local ethics committee approved the current study and each patient signed informed consent to undergo the experimentation, and acknowledging privacy measures.

Statistical Analysis

The prevalence of colposcopic lesions in the HIV-positive and HIV-negative groups was calculated using Chi-Square or Fisher test, to evaluate whether the prevalence of lesions was statistically different between the groups.

The HIV-positive group was also subdivided into two subgroups; each time, according to the different hypotheses under evaluation, we rated the frequency of lesions with Fisher's test. Differences between means were assessed with student's T-test for independent samples.

RESULTS

A total of 96 HIV-positive pregnant women were recruited but in 31 cases the clinical history and data were incomplete so only 65 women were finally enrolled in the study. The control group included 120 HIV-negative pregnant patients. The pregnant women included in the study were matched for age (p=0.221).

Prevalence of colposcopic and cytological lesions in HIV-positive and HIV-negative pregnant women

In the HIV-positive patients group the Pap-test was negative in 49 women (75%) and abnormal in the remaining 16 cases, of which 4 were ASCUS, 10 L-SIL and 2 H-SIL.

In the HIV-negative group the Pap-test was normal in 113 cases (95%) and positive in 7 cases: 4 ASCUS (3%) and 3 SIL (2%), of which 2 were L-SIL and 1 H-SIL. The difference in the frequency of lesions between the two groups, compared using Chi-square, proved statistically significant (p<0.001) (Table 3).

The colposcopic examination in the HIV-positive group was normal in 42 of 65 patients (64% of the cases) and pathological in the remaining 23 patients: 21 patients G1 (32%) and 2 patients G2 (4%).

In the HIV-negative patients 112 colposcopic examinations were judged as normal (93% of the group) while the remaining 8 cases were classified as G1 (7%). In none of these patients was there a G2 colposcopic lesion; therefore, the prevalence of colposcopic lesions was higher in the HIV-positive group, statistically confirmed by Chi-square (p<0.001) (Table 3).

One year after delivery the Pap-test was repeated in all women enrolled in the study.

In the HIV-positive group, the Pap-test was confirmed as stable in all 49 women with a primary negative sample and in 4 cases of SIL: 3 L-SIL and 1 H-SIL (managed with conisation); in one case we observed progression from H-SIL to carcinoma of the uterine cervix (managed with radical hysterectomy). For the remaining 11 women with ASCUS (4 cases) and L-SIL (7 cases), the Pap-test showed a regression of the primary lesion. Therefore, the prevalence of cytological lesions had reduced, one year after delivery, from 24.7% to 7.7% (Table 4).

Follow-up of HIV-negative patients showed normal cytology in 118 women: confirmed stable in all 113 women with a primary negative sample, regressed in 5 patients with a lesion diagnosed during pregnancy (3 ASCUS and 2 L-SIL); in 2 patients a colpocytological lesion was found to be still present but stable, without progression of the pathologic process: we observed one case of persistent ASCUS and one of H-SIL (managed with conisation).

Thus, also in the group of HIV-negative women, we observed a reduction of the prevalence of colpocytological abnormalities, one year after delivery, from 5.9% to 1.7% (Table 4).

The difference in regression of lesions between HIV-positive women (16.9%) and HIV-negative women (4.2%), resulted statistically significant (p=0.01).

Evaluation of risk factors for colposcopic and cytological lesions in HIV-positive pregnant women

Analysis of clinical history data showed a lower average parity (1.75 ± 1.53) in the HIV-positive group; regarding nationality, there were 45 Italian patients and 20 foreigners; HIV was sexually transmitted in 81.5% of patients, in 1 case (1.5%) there was vertical transmission, in 1.5% of women it was due to injectable drugs, in 6.1% of cases related to surgery or blood transfusions, 9.2% with an unknown contagion route (Table 1).

Clinical data showed that 93.8% of patients were in stage A, 1.5% in stage B and 4.7% had AIDS.

All HIV-positive women were treated with HAART during pregnancy, some of them (52.3%) were already receiving therapy before pregnancy, the remaining 47.7% started during pregnancy (Table 2).

In the same group, 11 women (16.9%) had a CD4+ T-cell count of less than 200 cells/μL while the remaining 54 patients (83.1%) had a higher CD4+ T-cell count. Meanwhile, 26 women (40%) had a high viral load (>1000 copies of viral genome/mL) and 39 pregnant patients (60%) showed a low viral load (Table 2).

All socio-demographic, clinical and laboratory features of HIV-positive court are listed in Tables 1 and 2.

The prevalence of colposcopic and cytological lesions identified in HIV-positive pregnant women was different in each group of patients stratified by CD4+ T-cell count, viral load, nationality and HIV-discordant partner, as statistically confirmed by the Fisher test. The Fisher test confirmed no difference in the prevalence of lesions according to other HIV-positive features, summarized in Tables 5 and 6.

DISCUSSION

Statistical analysis showed a higher prevalence of colpocytological abnormalities in HIV-positive pregnant women as compared to HIV-negative pregnant women (18% vs. 2.5%), in agreement with many studies in the international literature (9). This demonstrates a linkage between HIV infection and the presence of Pap-test abnormalities, thus confirming HIV-infection as a risk for colpocytological lesions during pregnancy.

One year after delivery, follow-up showed a reduction of lesions in both populations, although it was more significant in the HIV-positive group (dropping from 24.7% to 7.7%) than in the HIV-negative women (from 5.9% to 1.7%). According to this evidence, pregnancy itself results as an independent risk factor for Pap-test abnormalities; obviously, this risk is further increased by HIV infection. Data in literature are conflicting, as Minkoff et al. stated that pregnancy is not related to cytological lesions (10).

Our results can be explained by a transient depression of maternal cell-mediated immunity that allows the prevention of fetal rejection, inducing tolerance to the "non-self" fetal antigenic component of paternal derivation. In decidua and peripheral blood there is a shift from the Th1 to Th2 lymphocyte population.

The decrease of Th1 lymphocytes compromises cell-mediated reaction against intracellular pathogens, including HPV. This explains the greater prevalence of cytological and colposcopic lesions found during pregnancy (in both the HIV-positive and HIV-negative groups) as compared to results in the same women re-evaluated one year later (11).

A reduction in the prevalence of cytological lesion was observed in both patients groups but was statistically significant only for HIV-positive pregnant women, suggesting a synergy between HIV infection and pregnancy: together they promote immunosuppression and increase the risk of colpocytological lesions (12).

Analysis of the HIV-positive group showed a higher prevalence of cytological and colposcopic lesions in women with CD4+ T-cell count < 200 cells/μL. These data are in agreement with literature: usually the CD4+ T-cell count and viral load define the clinical stage of HIV+ patients; these parameters are also related to the development and progression of colpocytological lesions (13).

A link between a low CD4+ T-cell count and the prevalence of colposcopic alterations is clearly supported in literature, while the role of the viral load is still under debate (14,15).

Our data demonstrated a higher prevalence of cytological and colposcopic lesions in HIV-positive patients with a viral load >1000 gv/mL at the time of diagnosis; these results are in agreement with Kreitchmann et al., who gained the same evidence analysing a population of 898 HIV-positive women (16).

The HAART effect on cervical pathology is still uncertain: some authors reported a slower progression or an improved regression of lesions; others refuted this claim, asserting that HAART has no effect on HPV-related pathology.

We stratified patients according to the number of antiretroviral drugs they were taking, and our analysis proved that the number of drugs combined in HAART has no effect on the prevalence of colpocytological lesions. Likewise, the prevalence of lesions in women who started taking therapy before pregnancy was similar to the results in those who started therapy during pregnancy.

This evidence is justified by HIV's ability to persist in the genital mucosa (compartmentalization), inducing local immunodeficiency, even in women who are "responders" to antiretroviral therapy at the systemic level.

The prevalence of cytological abnormalities was greater in foreign pregnant women than Italian patients. This evidence probably results from the increasing number of women coming from areas where HPV screening is not done; most of these women had never undergone a Pap-test before.

In women with an HIV-concordant partner there was a lower prevalence of HPV-related abnormalities (cytological and colposcopic). This evidence

TABLE 1

Socio-demographic features of HIV-positive pregnant women (N=65).

HIV-positive features	N (%)
Nationality	
Italian	45 (69.2)
Foreign	20 (30.8)
Age	
Middle age (± SD)	30.14 (± 6.31)
Smoking status	
No	47 (72.3)
Yes	18 (27.7)
Educational level	
None	6 (9.2)
Primary school	11 (16.9)
Middle school	35 (53.8)
High school	12 (18.5)
University degree	1 (1.5)
Partner's infection	
HIV-discordant	28 (40)
HIV-concordant	26 (43.1)
Unknown	11 (16.9)
Contagion	
Sexual	53 (81.5)
Vertical	1 (1.5)
Surgery and transfusions	4 (6.1)
Injectable drugs	1 (1.5)
Unknown	6 (9.2)

TABLE 2

Clinical and obstetric features of HIV-positive pregnant women (N=65).

HIV-positive features	N. (%)
CDC stage	
A1,A2,A3	61 (93.8)
B,AIDS	4 (6.2)
Vaginal swab	
Negative	37 (56.9)
Positive	28 (43.1)
Therapy start	
Before pregnancy	34 (47.7)
During pregnancy	31 (52.3)
Pap-test	
Negative	49 (75.4)
ASCUS	4 (6.2)
L-SIL	10 (15.4)
H-SIL	2 (3.1)
Colposcopy	
G0	42 (64.6)
G1	21 (32.3)
G2	2 (3.1)
CD4+ T-cell count	
<200/uL	11 (16.9)
>200/uL	54 (83.1)
Viral load	
>1000 gv/mL	26 (40)
<1000 gv/mL	39 (60)
Co-infections	
No	60 (92.3)
Yes	5 (7.7)
Pregnancy outcomes	
Caesarean section	42 (64.6)
Spontaneous delivery	9 (13.3)
Miscarriage	4 (6.2)
Unknown	10 (15.4)
Gestational age at birth	
<37 week	21 (32.7)
>37 week	44 (67.3)

TABLE 3

Prevalence of cytological and colposcopic lesions in HIV-positive (N=65) and HIV-negative pregnant women (N=120).

	PAP-test negative (%)	ASCUS/L-SIL/H-SIL (%)	p-Value	G0 (%)	G1/G2 (%)	p-Value
HIV+ (N.65)	49 (75.3)	16 (24.7)	<0.001	42 (64.6)	23 (35.4)	<0.001
HIV- (N.120)	113 (94.1)	7 (5.9)		112 (93.3)	8 (6.7)	

TABLE 4

Follow-up, one year after delivery, of Cytological lesions found in HIV-positive (N=65) and HIV-negative women (N=120).

Follow-up of cytological lesions	HIV-positive (N.65) (%)	HIV-negative (N.120) (%)	p-Value
Regression	11 (16.9)	5 (4.2)	0.01
Stability or evolution	5 (7.7)	2 (1.7)	NS

can be explained by a more responsible sexual behaviour of HIV-positive patients: when sensitized, they are more conscious and careful, reducing the number of sexual partners (one of the main risk factors of HPV infection) and insisting on the use of condoms, to avoid co-infection with different HIV genotypes. This behaviour obviously also prevents HPV-coinfection and related lesions.

Limits of the study include the restricted number of patients enrolled but it is difficult to overcome this limit because fortunately, relatively few pregnant women are affected by this disease in Italy. Probably a longer follow-up may increase our knowledge about the long-term evolution of colpocytological lesions.

TABLE 5

Prevalence of cytological and colposcopic lesions in HIV-positive pregnant women stratified by socio-demographic features (N=65).

Characteristics	PAP-test negative	ASCUS/L-SIL/H-SIL	p-Value	G0	G1/G2	p-Value
Nationality						
Italian	38	7	0.02	35	10	0.002
Foreign	11	9		7	13	
Sexual transmission						
Yes	39	14	NS	34	19	NS
no	4	1		2	3	
Smoking status						
No	35	14	NS	31	16	NS
Yes	12	4		11	7	
Educational level						
Middle school	40	12	NS	33	19	NS
High school or university degree	9	4		9	4	
Partner's infection						
HIV-concordant	22	4	0.048	23	3	0.001
HIV-discordant	17	11		13	15	
Age						
< 31	26	11	NS	21	16	NS
>31	23	5		21	7	
Parity						
<3	44	5	NS	37	5	NS
>3	13	3		20	3	

TABLE 6

Prevalence of cytological and colposcopic lesions in HIV-positive pregnant women stratified by clinical and obstetric features (N=65).

Characteristics	PAP-test negative	ASCUS/L-SIL/H-SIL	p-Value	G0	G1/G2	p-Value
CD4+ T-cell count						
<200/uL	5	6	0.02	4	7	0.048
>200/uL	44	10		38	16	
Viral load						
<1000 gv/mL	34	5	0.009	29	10	0.046
>1000 gv/mL	15	11		13	13	
Vaginal swab						
Positive	29	8	NS	22	15	NS
Negative	20	8		20	8	
CDC stadium						
A1,A2,A3	47	14	NS	41	20	NS
B,AIDS	2	2		1	3	
Therapy start						
During pregnancy	22	9	NS	19	12	NS
Before pregnancy	26	7		22	11	
Co-infections						
No	45	15	NS	40	20	NS
Yes	4	1		2	3	
Pregnancy outcome						
CS,SD						
Miscarriage	39	12	NS	33	18	NS
	3	1		3	1	
Gestational age at birth						
<37 weeks			NS			NS
>37 weeks	9	5		7	7	
Birth weight						
<2800 g	17	6	NS	13	10	NS
>2800 g	25	7		23	9	
Apgar 5'						
<9	7	3	NS	7	3	NS
>9	35	10		29	16	

CONCLUSION

The current study demonstrates a higher prevalence of cytological and colposcopic alterations in HIV-positive pregnant women, confirming them as an "at-risk population" for HPV-related cervical abnormalities. Meanwhile, it is well known that the success of prevention depends strictly on patients' compliance to screening programs. Finally, pregnancy emerges as the best period to inform women about the importance of screening for cervical cancer prevention purposes.

Our results revealed immunosuppression and a high plasma viral load as independent risk factors for cervical abnormalities during pregnancy. This

confirms the need for an optimal management of HIV infection, with the best HAART and a personalized screening program, especially in patients identified as a "high risk" (according to the viral load and CD4+ T-cell count).

These results are in agreement with previous reports in literature; in addition, this study identifies two new features in HIV-positive pregnant women, related to the prevalence of colpocytological lesions never previously recognized. The higher prevalence of lesions in HIV-positive foreign pregnant women underlines the need to pay particular attention to women coming from areas where HPV-screening is not well established. An "HIV-concordant partner" seems to be a protective factor against HPV cervical abnormalities in HIV-positive women, encouraging a more responsible sexual behaviour and close screening of women with an HIV-discordant partner.

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