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mini-review

A risk-stratified approach to labour and delivery in HIV-infected women in a large tertiary Hospital in the North of Italy

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SUMMARY: **A risk-stratified approach to labour and delivery in HIV-infected women in a large tertiary Hospital in the North of Italy.**

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The management of HIV-infected woman who became pregnant needs the collaboration of different and complementary medical experts in order to minimize the risk of mother-to-child transmission of HIV. Currently, vaginal delivery must be guaranteed to all HIV-infected women in whom this choice is considered safe.

The aim of our paper is to describe the organization of a large tertiary acute-care teaching hospital of Northern Italy with a total of 262 deliveries from 231 HIV-infected women between 1985 and 2014. A multidisciplinary team (MDT) has developed a risk-stratified three categories approach to labour and delivery in HIV-infected women in order to improve patient's care and management.

KEY WORDS: Labour - Delivery - HIV-infected women.

Introduction

The optimal management of pregnancy, labour and delivery in HIV-infected women should be shared between different and complementary specialists (gynecologists and obstetrics, infectious disease specialists, pediatrician, midwives, psychologists) in order to improve patient's care and management.

The introduction of early initiation of antiretroviral therapy (ART) allows to achieve a persistent HIV-RNA suppression in a large number of patients, minimizing the risks of mother-to-child transmission (MTCT) of HIV during pregnancy and delivery (1, 2). However, ART related toxicities involve a risk of renal and hepatic disfunction, dyslipidaemia and diabetes that therefore must be checked during the whole duration of pregnancy (3, 4).

National and international guidelines confirm the opportunity and feasibility of vaginal delivery for HIV-infected women with HIV RNA <50 copies/ml (5, 6). However, a previous paper underlined how the clinical practice does not always reflect recommendations, generating an amount of unnecessary caesarean section (CS) in women without a clear indication (7).

On the other side, not all women arrive to delivery with HIV RNA <50 copies/ml and so they require a specific management to decrease the risk of MTCT. The use of a specific, standardized and common management for pregnancy, labour and delivery in each maternal-fetal department could reduce the number of unnecessary CS without increasing the risk of MTCT.

The aim of our paper is to describe the obstetrical

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management of HIV-infected women in our large tertiary acute-care teaching hospital through an easy protocol, developed by our multidisciplinary team (MDT) (gynecologists-obstetrics, infectious diseases specialists, pediatrician, midwives and psychologists), that allow a quick stratification of risk of MTCT in HIV infected women.

Premise

This protocol was conceived for a 1,300-beds tertiary adult acute-care teaching hospital: "Policlinico San Martino" Hospital in Genoa, Italy (8).

The "Policlinico San Martino" accounts about 1,600 births per year and represents a third-level center and one of the referral hospitals for pregnancies in HIV infected women in Liguria region.

From 1985 to 2014, a total of 262 deliveries from 231 HIV-infected women were assisted at "Policlinico San Martino Hospital".

Stratification risk

This protocol, developed by our MDT, is based on a stratification of HIV infected patients into three categories, based on the risk of MTCT. To stratify the risk of HIV MTCT, we considered the parameters described in Table 1.

Three categories of HIV infected patients were identified following risk factors mentioned in Table 1: low-risk, medium-risk and high-risk HIV MTCT (Table 2).

Management of pregnancy (valid for each category)

Follow-up in pregnancy was scheduled as monthly obstetric visits until 34th week and then every two weeks until the end of pregnancy. An infectious disease specialist visit was performed every three months aiming at HIV-RNA suppression (HIV-RNA below 50 copies/ml) in the 3rd trimester for at least 4 weeks before delivery. Depression' assessment through questionnaires and interviews with psychologists was performed twice during pregnancy (Figure 1).

During the third trimester, the following delivery options were selected according to the risk of HIV-MTCT: spontaneous vaginal delivery, vaginal induced delivery, elective CS and, eventually, prepartal and intrapartal pharmacological treatment with zidovudine (AZT). The indications relating to labour and delivery will be provided in detail in the sections below according to the division into three categories described in Table 2. The possible modalities of delivery should be shared and discussed with the patient at each obstetrical visit during the pregnancy in

TABLE 1 - PARAMETERS TO STRATIFY THE RISK OF HIV MTCT.

Diagnosis of HIV	Known (or with HIV diagnosis within the first trimester of pregnancy)
	HIV diagnosis in the second trimester of pregnancy
	HIV diagnosis peripartum (< 4 weeks) or in labour
HIV-RNA load for at least 4 weeks before delivery	Less than or equal to 50 copies/ml
	More than 50 copies/ml
CD4+ cell count for at least 4 weeks before delivery	More than or equal to 200 cell/mmc
	Less than 200 cell/mmc
Uncomplicated pregnancy	Yes
	No
Regular follow-up during pregnancy	Yes
	No
Patient compliance (ability to understand and follow medical indications thanks also to a favourable social context)	Yes
	No
Motivation to have vaginal delivery	Yes
	No

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TABLE 2 - CATEGORIES OF HIV MTCT RISK.

LOW RISK	***All the following criteria***
	Known HIV diagnosis (or at most diagnosis within the first trimester of pregnancy)
	Effective ART therapy (stable HIV-RNA <50 copies / ml, CD4 + > 200 cell / mm^3) for at least 4 weeks before delivery
	Regular follow-up during pregnancy, good compliance and understanding
	Uncomplicated pregnancy
MEDIUM RISK	***At least one of the following criteria***
	Complicated pregnancy (any condition that imposes the need to anticipate the timing of childbirth or carries an increased risk of fetal infection)
	HIV diagnosis in the second trimester of pregnancy
	Poor compliance or inability to understand and follow medical indications
HIGH RISK	***At least one of the following criteria***
	HIV diagnosis peripartum (< 4 weeks) or in labour
	Not effective ART therapy (HIV-RNA >50 copies/ml, CD4 + < 200 cells/mm^3) in the last 4 weeks before delivery or patient not in ART therapy
	Known multi-drug resistant virus
HIGH RISK (special category)	Unknown HIV status in patient with history of risky behaviours in active labour

	A little of the time	Some of the time	Good part of the time	Most of the time
1. I feel down hearted and blue.	○	○	○	○
2. Morning is when I feel the best.	○	○	○	○
3. I have crying spells or feel like it.	○	○	○	○
4. I have trouble sleeping at night.	○	○	○	○
5. I eat as much as I used to.	○	○	○	○
6. I still enjoy sex.	○	○	○	○
7. I notice that I am losing weight.	○	○	○	○
8. I have trouble with constipation.	○	○	○	○
9. My heart beats faster than usual.	○	○	○	○
10. I get tired for no reason.	○	○	○	○
11. My mind is as clear as it used to be.	○	○	○	○
12. I find it easy to do the things I used to.	○	○	○	○
13. I am restless and can't keep still.	○	○	○	○
14. I feel hopeful about the future.	○	○	○	○
15. I am more irritable than usual.	○	○	○	○
16. I find it easy to make decisions.	○	○	○	○
17. I feel that I am useful and needed.	○	○	○	○
18. My life is pretty full.	○	○	○	○
19. I feel that others would be better off if I were dead.	○	○	○	○
20. I still enjoy the things I used to do.	○	○	○	○

Figure 1 - Depression test.

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order to reduce the risk of discomfort and low compliance. The patient and the family members, who wish to be present at the birth, should know that all hospital staff is required to wear personal protection devices (precaution measures, such as mask and glasses) during labour and delivery. This situation could represent an element of risk in the protection of the patient's privacy, as these devices are not always worn in the delivery of patients with negative serology.

The patient should be informed that she must go immediately to the hospital in case of PROM.

Maternal breastfeeding in HIV infected women is to avoid. Lactation inhibition should be timely performed with Cabergoline tablets 1 mg, single dose. Instead skin to skin without breast attachment or, as alternative, skin to skin with the father should always be allowed.

Antibiotic prophylaxis (first generation cephalosporin, e.g. cefazoline 2 g ev every 8h or similar molecules) in puerperium should be administered in the presence of episiotomy or extensive vaginal tears or if a CS is performed.

During puerperium, ART should be continued, patients' privacy should be maintained and hospitalization should be extended until the seventh day. A counselling about future contraceptive method and vaccination for rubella, Hepatitis B and chicken pox viruses should be performed.

A dedicated psychological counselling should be performed to find early signs of depressive disorders in order to avoid postpartum depression.

Management of labour and delivery (stratified according to MTCT risk)

Low risk

In the low-risk patients (Table 2), vaginal delivery should always be proposed and encouraged in the presence of the following helpful obstetric conditions:

- age between 18 and 45 years
- single fetus
- cephalic presentation
- no previous CS
- gestational age over 34 weeks
- premature rupture of membranes (PROM) for <12 hours.

In case of low-risk patients (Table 2) without the above described favourable obstetric conditions, the modality of delivery should be discussed between the MDT and the patient.

Our MDT decided that the last term of pregnancy to await the onset of spontaneous labour is 41 weeks +3 days of gestational age. At 41 weeks +3, the single case should be evaluated by the MDT and the induction of labour with prostaglandins should be performed. We generally use Dinoprostone 10 mg vaginal delivery system to induce labour. Disconnecting the amniotic membranes for the labour's induction is contraindicated. CS must be performed if the patient is not motivated to have vaginal delivery or if there are contraindications to induction.

Hepatitis C virus co-infection (HCV/HIV), as well as hepatitis B virus co-infection (HBV/HIV), in the absence of secondary hepatic impairment does not change the woman's peripartal management (9).

AZT administration is not recommended to decrease the risk of MTCT neither during vaginal delivery nor in CS. The regular intake of oral ART therapy and to limit invasive action during labour is recommended.

As concerning the management of PROM, we suggest the following clinical practices:

1) PROM at ≥ 37 weeks: immediate induction of labour with prostaglandines. If the patient is not in active labour after 12 hours from the PROM, CS is recommended.
2) Preterm PROM (pPROM) < 37 weeks: the obstetrical management should be discussed by MDT. We propose to perform a CS within 12 hours from PROM, after a single dose of betamethasone 12 mg for fetal lung maturation. Alternatively, CS should be immediately performed after the second dose of betamethasone 12 mg that should be administered after 12 hours from the first (short cycle).

In case of pPROM > 34 weeks and in presence of helpful obstetric conditions, induction of labour with prostaglandines can be evaluated by MDT. If the patient is not in active labour after 12 hours from the PROM, CS is recommended.

Medium risk

There is not an absolute contraindication to vaginal delivery in medium risk patients (Table 2), but the obstetrical management should be discussed by MDT. If the HIV-RNA is stably <50 copies/ml and

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CD4+T lymphocyte count is > 200 cell/mm^3 for at least 4 weeks before delivery, the vaginal delivery could be proposed.

In the case of a complicated pregnancy that requires to anticipate the timing of delivery, after 34 weeks, if the HIV-RNA is stably <50 copies/ml and CD4+T lymphocyte count is > 200 cell/mm^3 for at least 4 weeks before delivery, the use of prostaglandins to induce labour can be evaluated by the MDT.

AZT administration is not recommended to decrease the risk of MTCT neither in vaginal delivery nor in CS if the HIV-RNA is stably <50 copies/ml and CD4+T lymphocyte count is > 200 cell/mm^3 in the last 4 weeks before delivery. Otherwise AZT administration must be discussed by MDT.

In case of PROM (> 37 weeks) the birth should always not be delayed over 12 hours. If HIV RNA is <50 copies/ml, CD4+T lymphocyte count is > 200 cell/mm^3 at least for 4 weeks before delivery and in presence of helpful obstetric conditions, induction of labour with prostaglandines can be evaluated. CS should be timely performed in absence of above-mentioned conditions. If the patient is not in active labour after 12 hours from the PROM, CS is always recommended. In case of pPROM CS should be performed within 12 hours from PROM, after a single dose of betamethasone 12 mg.

High risk

In high risk patients (Table 2), vaginal delivery is contraindicated.

Planned CS section during the 39th week should be performed. ART therapy should be continued or started as early as possible in patients who are not yet under treatment (indicated by an infectious disease specialist), preferably with emtricitabine/tenofovir disoproxil fumarate + raltegravir, or + atazanavir/ritonavir (9).

AZT should be administered in prophylaxis, in order to minimize MTCT, at 2 mg/kg, in slow infusion (about 4 hours) to be completed before the CS begins, if possible, followed by AZT at 1 mg/kg in rapid infusion during CS section (about 30 minutes). Infectious disease specialist should be consulted in order to administrate intrapartal nevirapine (9).

Unknown HIV serology in women presenting an active labour or imminent delivery, who live in a social context at high risk of infection (detention, drug abuse, alcoholism, HIV-infected partner, irregular immigration) should be undergone following care to decrease MTCT risk:

- immediate urgent serology
- involvement of neonatologist and infectious disease specialist to discuss possible use of intrapartal AZT
- vaginal delivery assistance, if active labour and serology not yet available
- skin to skin without breast attachment, if serology not yet available.

Discussion

The number of persons living with HIV worldwide reached approximately 36.9 million in 2017 (WHO), with an increase in prevalence compared to past years, also due to longer life expectancy in people on antiretroviral treatment and decline in AIDS-related deaths (10). As a consequence, there is also a large population of young HIV infected women who wish to become pregnant and to perform a vaginal delivery. So a specific and optimal management of each pregnant women living with HIV is need in order to prevent HIV MTCT and for the welfare of the mother herself.

First of all, infected HIV women wishing to conceive in the near future, should carry out a pre-conceptional counselling with gynecologist and infectious diseases specialist discussing the optimal management of HIV during the pregnancy. Patients already treated with a good response, should continue the current ART stopped the potential teratogenic antiretrovirals (dolutegravir) or drugs not studied during pregnancy (tenofovir alafenamide and cobicistat) (11-15). If the patient is not being treated, an ART regimen consisting of at least 3 drugs must be promptly offered, with the goal of reaching HIV RNA <50 copies/mL as quickly as possible if treatment is initiated during pregnancy, or maintain undetectable viremia if ART therapy was already in place (9, 11).

The patient should immediately be taken in care by MDT, which also includes psychological support during pregnancy and after childbirth. Sometimes women may experience significant psychosocial barriers to accessing HIV care such as HIV-related stigma, unemployment and lack of financial resources. Furthermore, the prevalence of postpartum depres-

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sion among women living with HIV is greater than in the general population and in high-income settings is reported to be between 30 and 53% (9, 11).

In the women treated with ART, the choice of type of delivery should be made between 34-36 weeks and after plasmatic dosage of HIV-RNA load. Vaginal delivery is recommended in women with a plasma HIV load of < 50 HIV RNA copies/mL and CD4+>200 cell/mm^3 at 34-36 weeks, in the absence of obstetric contraindications. Traditionally amniotomy, fetal scalp electrodes and blood sampling, instrumental delivery and episiotomy have been avoided in HIV infection because of theoretical transmission risks. Data from the pre-ART era have been reviewed and show little or no risk for many of these procedures. Data from the ART era are scant. The use of vacuum assisted delivery during operative vaginal delivery should be limited (9, 13).

Planned CS section is recommended in women with a plasma viral load >50 HIV RNA copies/mL at 36 weeks (9, 13).

In all cases of PROM, delivery should not be delayed, in order to minimize MTCT. The induction of labour with prostaglandins is recommended if viral load <50 HIV RNA copies/mL. Instead, immediate caesarean section should be considered if plasma viral load > 50 HIV RNA copies/mL during last measure (9, 13-15).

Concerning increased MTCT risk during prolonged PROM, there is not a definite conclusion in literature. The duration of ruptured membranes analyzed is not uniform and there are no randomized control trials that consider the viral load at birth in ART era (13).

In the pre-ART era several studies suggested that prolonged duration of ruptured membranes, usually analyzed as greater than 4 hours, in women who were either untreated or treated with AZT monotherapy, resulted in a significantly increased risk of vertical transmission. There are few published studies from ART era. A study from Spain of 500 HIV-positive women examined the effect of various obstetric risk factors on vertical transmission rates in women untreated, in monotherapy or dual therapy, and finally in those on cART. PROM > 6 hours compared to < 6 hours was only significantly associated with vertical transmission in the group of untreated women (26.6 *vs* 11.9%; P=<0.01) (16). Also a recent prospective study of 46 PROMs in HIV positive women concluded that in women who have received optimal therapy, PROM does not represent a risk factor for fetal transmission (9, 13, 17, 18).

In conclusion, the duration of PROM does not seem to represent a significant risk factor for vertical transmission in low-risk group.

The management of pPROM at ≥34 weeks is the same as term PROM, induction of labour with prostaglandins can be evaluated in case of undetectable viral load. When pPROM occurs at < 34 weeks intramuscular steroids should be administered, in accordance with national guidelines, and multidisciplinary discussion should be performed about the timing and mode of delivery (9).

Corticosteroid prophylaxis is most effective after 48 hours and within 7 days, however it reveals an efficacy trend already after 24 hours from the first dose and has biological effect after a few hours. Recent evidence suggests the possibility of shortening the interval time between the two doses of betamethasone to 12 hours instead of 24 (19).

AZT intrapartum is recommended in case of viral load >50 HIV RNA copies/mL. Addition of nevirapine in a single dose at delivery to enhance a combination regimen does not appear to be recommendable due to absence of significant additional benefit (9).

We realized, based on this recent literature, an easy internal protocol to improve our clinical practice. Our three categories risk stratification show that the risk of MTCT of HIV depends on several parameters and obstetrical management must be specific for each class of risk.

A good quality of life during pregnancy must be guaranteed to all women, ensuring them the privacy and the support they need. HIV infected patients should be reassured about the possibility of reaching undetectable HIV viral load through ART therapy and to perform a vaginal delivery with a very low probability of MTCT. HIV must be considered a chronic disease that can be controlled by a proper therapy.

Conclusions

It is important to support the right of HIV infected women to become pregnant, ensuring them a good quality of life during pregnancy and an optimal and safe management of labour and delivery. MDT and easy and common protocol represent useful tools for the management of these women in order to minimize the risk of MTCT improving patients' care during pregnancy, labour and delivery.

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