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Metabolic Alterations in HIV-Infected Pregnant Women: Moving to Metabolic Tailoring of Antiretroviral Drugs

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Abstract

The most striking effect of increased survival and improved quality of life in HIV-infected women undergoing antiretroviral therapy is the feasibility of motherhood-desire satisfaction. However, such advantages are often associated with drug-related metabolic toxicities, particularly relevant in the pregnancy context.

Recent guidelines provide recommendations and trends for the use of antiretroviral therapy in pregnant women, but current literature falls short of providing specific insights on the need for metabolic monitoring and treatment in HIV-infected pregnant women.

In this review we provide specific insight into the state-of-the-art of: detection, evaluation, and management of metabolic alterations in this special population.

Pregnancy is in fact a metabolic transition process, potentially associated with specific diseases in the mother, in the newborn, and in the adulthood of the child. We will not simply discuss antiretroviral therapy metabolic toxicities, but rather their interaction with the physiological metabolic changes occurring during pregnancy.

Close monitoring is needed to diagnose metabolic alterations that can lead to adverse outcomes in the mother, in the newborn, and potentially in adulthood.

Lifestyle interventions and an appropriate metabolic tailoring of antiretroviral therapy drugs need to be considered in the prevention and treatment of metabolic alteration during pregnancy. **(AIDS Rev. 2014;16:14-22)**

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Key words

Pregnancy. Prevention. HIV. Metabolism. Antiretroviral therapy.

Introduction

The most striking effect of improved quality of life in HIV-infected women undergoing antiretroviral therapy (ART) is the feasibility of motherhood-desire satisfaction. Antiretroviral therapy is able to dramatically reduce the vertical transmission of HIV infection to < 1% in a non-breastfeeding population, proving the capability of HIV treatment for prevention.

However, such advantages are often associated with drug-related metabolic toxicities, which are particularly relevant during pregnancy.

Recent guidelines[1,2] and several recent papers[3-6] have provided recommendations and opened new scenarios for the use of ART in pregnant women.

Nevertheless, current literature falls short of providing specific insights into the requirement for metabolic monitoring and treatment in HIV-infected pregnant women.

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The cultural background that moved the interpretation of metabolic alterations from ART-related toxicities to the complex interplay of host, virus, and drug risk factors needs to be readjusted in the pregnancy setting. We will not simply discuss ART metabolic toxicities, but rather their interaction with the physiological metabolic changes occurring during pregnancy.

The aims of this review are:

- To review metabolic changes during pregnancy and describe their impact both in the mother and the newborn
- To discuss how to monitor/deal with the clinical management of metabolic disorders
- To discuss the metabolic tailoring of ART in pregnant women

Search strategies and selected criteria

Data from this review were identified by searches of MEDLINE, references from relevant articles, DHHS, EACS, and IAS guidelines and abstract books of the most prestigious International Conference on HIV. Search terms were "pregnancy", "HIV", "metabolic", "antiretroviral therapy". Only studies reported in the English language were included.

Metabolic changes during pregnancy and their impact in both mother and newborn

Physiological metabolic changes during pregnancy

In response to the increased demands of the rapidly growing fetus, pregnant women undergo, from the second trimester, metabolic changes involving proteins, glucose, and lipids.

Lipid changes

In the setting of HIV-infected pregnant women, the evolution of lipid levels across a quarterly progression in HIV-infected pregnant women was investigated by Floridia, et al.[7] in a cohort of 248 women. Interestingly, unlike other lipids, the total cholesterol/HDL cholesterol ratio remained substantially unchanged during pregnancy (mean values at first, second, and third trimester: 3.50, 3.32, and 3.50, respectively), making it difficult to establish the cardio-metabolic impact of these changes with regard to cardiovascular risk or simply to endothelial dysfunction.

Triglyceride (TG) levels measured at mid-pregnancy or at the third trimester in the aforementioned HIV-infected pregnant women[7] were independent predictors of neonatal birth weight, suggesting a potential independent role in the development of fetal macrosomia.

In a more recent study conducted in the setting of HIV-infected pregnant women, previous history of lipodystrophy was associated with significantly higher TG values at all pregnancy trimesters. In multivariate analyses, lipodystrophy independently increased the risk of hypertriglyceridemia threefold at the first trimester and eightfold at the second and third trimesters[8].

Body fat changes frequently associated with HIV infection therefore represent an additional risk factor to add to physiological alterations. It is necessary to identify potential mechanisms and genetic or biochemical markers which could be helpful in identifying women at risk of metabolic abnormalities.

Protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI) are associated with lipid concentrations and TG and total cholesterol (TC) values. Women on PI treatment appear to have significantly higher TG values at all trimesters compared to women not on PI treatment at the same gestational age[7]. Treatment with PIs had a less pronounced effect on TC, as observed for TG. In the same case series from Floridia, et al.[7], compared to women on PIs, women on non-PI-based ART (mostly represented by three-drug regimens) had significantly lower TG levels at all trimesters (112.7, 171.1, and 228.3 mg/dl, respectively; $p = 0.009$, 0.021, and 0.001). Conversely, no significant differences in TG levels were observed between women on non-PI-based ART and women not on ART who had levels of 97.4 and 153.4 mg/dl at the first and second trimester, respectively ($p > 0.05$).

A similar analysis based on a stavudine-containing regimen showed higher values of TG (mean difference: 45.0 mg/dl; 95% CI: 6.8-83.4; $p = 0.022$) and TC (mean difference: 19.5 mg/dl; 95% CI: 2.3-36.7; $p = 0.027$) at the first trimester of gestation only[7].

Glucose changes

The prevalence of gestational diabetes mellitus (GDM) is increased in patients with HIV infection[9-11], and it appears to increase in the ART era. This trend

may be the result of the higher prevalence of traditional risk factors for GDM, but also the direct and indirect effects of ART[11,12]. In addition, residual systemic inflammation, observed in patients with suppression of HIV viral load as well, may contribute to the pathogenesis of GDM with a unique pathophysiological mechanism[13].

Insulin resistance is a well-recognized complication of first-generation PI and/or thymidine analogue therapy, and it may result from inhibition of glucose uptake by adipocytes and impaired insulin secretion by pancreatic beta-cells[14-18].

Two prospective, multicenter cohort studies in the Women's Interagency HIV Study were designed to assess the association between ART and the incidence of diabetes mellitus (DM). The first was conducted from 1995 to 1998[19] and the second from 2000 to 2008[20] on a total 1,785 and 2,088 non-pregnant women, respectively. Protease inhibitors were associated with a threefold increase in the incident risk of DM in the former and cumulative exposure to NRTI was associated with increased incidence DM in the latter.

In a multicenter, prospective observational study, 149 HIV-infected pregnant women were assessed for insulin, glucose, and C-peptide evaluated at fasting state and one hour after a 50 g glucose test. Impaired glucose tolerance (IGT) was defined as a one-hour glucose > 130 mg/dl. Impaired glucose tolerance and pregnancy outcomes were compared between those taking PIs and those not. Fifty-seven out of 149 subjects (38%) had IGT. Body mass index (BMI), Hispanic ethnicity, and maternal age, but not PIs, were associated with IGT. There were no differences in insulin resistance, beta-cell function, or pregnancy outcome associated with PI use[21].

Hepatitis C virus (HCV) infection is a strong independent risk factor for insulin resistance and DM[22] in HIV-infected patients. This is confirmed in HIV-infected pregnant women, as shown in a study of 78 women with no history of DM or glucose metabolism abnormalities (GMAs)[23]. During pregnancy, GMAs were observed in 20 women (25.6%; GDM: 6, 7.7%; IGT: 14, 17.9%). In a multivariate analysis, after adjusting for age and ongoing ART (PI or nevirapine), GMAs were significantly associated with HCV coinfection (adjusted OR: 4.16; 95% CI: 1.22-14.1; p = 0.022).

The American Diabetes Association, in the context of worrisome worldwide increases in obesity and diabetes rates, has been devising new diagnostic criteria for GDM, with the intent of optimizing gestational outcomes for women and their babies[24].

Vitamin D changes

Vitamin D is essential for the health of pregnant women and their infants. Vitamin D deficiency during pregnancy is reflected in lower maternal weight gain and biochemical evidence of disturbed skeletal homeostasis in the infant, with, in extreme situations, reduced bone mineralization and radiologically evident rickets. Populations at risk for vitamin D deficiency are those for which, for environmental, cultural, or medical reasons, exposure to sunlight is poor and the dietary intake of vitamin D is low[25].

In the setting of HIV-infected pregnant women, low vitamin D status appears to have a negative effect on HIV disease progression and mortality in resource-limited settings[26]. In a small recent U.S. study by Ross, et al., 16 HIV-1-infected pregnant women and 24 HIV-uninfected pregnant controls were enrolled prospectively. In multivariable regression, no variables, including treatment group, were predictive of vitamin D level. Although there was no difference in vitamin D levels between HIV-infected pregnant women and controls, both groups had a high prevalence of vitamin D deficiency[27].

In a cross-sectional study among adult HIV-infected participants, Guaraldi, et al. demonstrated an association between vitamin D deficiency and DM[28].

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study assessed the associations between maternal vitamin D concentration and glucose metabolism in a cohort of 399 pregnant women living in an Australian subtropical environment[29].

All patients underwent a blinded 75 g oral glucose tolerance test. Mean serum 25-hydroxy vitamin D was 132.5 ± 44.0 nmol/l. A difference of one standard deviation (SD) in maternal 25-hydroxy vitamin D was inversely related to fasting glucose (fasting glucose lower by 0.05 mmol/l; p = 0.012) when assessed with multiple linear regression after adjusting for confounders. Maternal 25-hydroxy vitamin D correlated with β-cell function as estimated by the log-transformed homeostasis model assessment-β-cell function equation (r = 0.131; p = 0.009), but not with the homeostasis model assessment of insulin resistance. The author concluded that an association between mid-gestational 25-hydroxy vitamin D and fasting glucose was confirmed in a largely normoglycemic and

vitamin D-replete pregnant population. The correlation between 25-hydroxy vitamin D and β-cell function suggests that vitamin D may influence glucose metabolism through this mechanism. Intervention studies are required to determine causality and the role of vitamin D replacement in deficient individuals.

Transferability of these findings in pregnant HIV-infected women is not known.

Impact of metabolic changes in the mother

The aforementioned metabolic disorders have been recognized in the pathogenesis of endothelial dysfunction and hepatic impairment recognized in some pregnancy-related diseases, in particular hypertensive and liver disorders.

Hypertensive disorders in pregnancy

Hypertensive disorders complicating pregnancy commonly contribute greatly to maternal morbidity and mortality. There are five types of hypertensive disease: gestational hypertension, chronic hypertension, preeclampsia, eclampsia, and preeclampsia superimposed on chronic hypertension.

During a normal pregnancy, dramatic changes in the cardiovascular system and consequently in renal function occurs, and endothelial dysfunction has been recognized as the possible pathological mechanism of hypertensive disorder in pregnancy[30].

In HIV-infected women, data on endothelial dysfunction during pregnancy are still limited. Luzi, et al., in a prospective longitudinal study, investigated endothelial function in 14 consecutive HIV-infected pregnant women and 19 HIV-negative pregnant women. The authors did not find any significant change in flow-mediated dilation during pregnancy and between groups. Pregnancy does not appear to further increase the cardiovascular disease risk associated with HIV infection. More studies are needed to determine if HIV status affects endothelial function and flow-mediated dilation during pregnancy[31].

Liver Diseases

Abnormal liver tests occur in 3-5% of pregnancies, with many potential causes. However, most liver dysfunctions in pregnancy are pregnancy-related and caused by one of the five liver diseases unique to the pregnant state: *hyperemesis gravidarum*, intrahepatic cholestasis of pregnancy, preeclampsia, "HELLP" syndrome, and acute fatty liver of pregnancy. These fall into two main categories depending on their association with or without preeclampsia–

Metabolic changes in the newborn

A well-known indicator of the newborn nutrition is birth weight[32]. Low birth weight has been defined by the World Health Organization (WHO) as weight at birth of less than 2,500 g[33]. This cutoff for international comparison is based on epidemiological observations that infants weighing less than 2,500 g are approximately 20-times more likely to die than heavier babies[34].

Birth weight is a surrogate marker of the mother's nutrition during pregnancy and of a newborn's chances of survival, growth, and psychosocial development[32]. It is now accepted that maternal over/under-nutrition could "program" serious illnesses in adulthood on a long-term basis, in particular metabolic syndrome, cardiovascular diseases, and DM[35,36].

The outcomes of pregnancy follow a U-shaped curve with more adverse outcomes in women starting pregnancy underweight or overweight/obese compared with those of normal weight. The U-shaped curve represents the relationship between perinatal nutrition and subsequent risk of metabolic syndrome and of developing obesity coming from both under- and over-nutrition in the perinatal period[37].

Underweight

In the HIV setting, factors influencing gestational age-adjusted birth weight have been analyzed in a National Series of 600 newborns[38]. Compared to newborns from HIV-negative women, newborns from HIV-infected women had significantly lower absolute birth weight (2,799 vs. 2,887 g; $p = 0.007$) and birth weight *Z* score (–0.430 vs. –0.222; $p < 0.001$). The only maternal characteristics associated with significantly lower *Z*-score below the 10th percentile in the multivariate analysis were recent substance use (adjusted OR: 3.17; 95% CI: 1.15-8.74) and smoking (adjusted OR: 2.26; 95% CI: 1.13-4.49).

Overweight

In pregnant HIV-infected women, glucose values below the threshold usually defining hyperglycemia

Table 1. How to monitor and deal with clinical management of metabolic disorders in HIV-infected pregnant women

Metabolic parameters	Frequency	Type of intervention	ART
Fasting TC, HDL, LDL, TG	Monthly	Lifestyle habits	Switching
Fasting glucose	Monthly	Lifestyle habits	Switching
OGTT 75 g	24-28 week	Diet and use of insulin if GDM	Switching
Vitamin D assessment	Basal only if not routinely supplemented	10 µg vitamin D in population at risk for deficiency	
Blood pressure, weight and proteinuria	Monthly	Antihypertensive therapy (avoid angiotensin converting enzyme-inhibitors); Preterm delivery in severe cases	
Liver function test, transaminases and lactate levels	Monthly	Ursodeoxycholic if maternal cholestasis; Preterm delivery in severe cases	Switching to less hepatotoxic drug in severe cases

ART: antiretroviral therapy; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; OGTT: oral glucose tolerance test.

were associated with an increased risk of delivering large-for-gestational age infants[39].

How to monitor/deal with clinical management of metabolic disorders in HIV-infected pregnant women

These recommendations are summarized in table 1.

Clinical management of metabolic disorders in HIV-infected pregnant women is the same as that suggested in HIV-infected non-pregnant individuals. It includes lifestyle and pharmacological approaches similar to the general population as well as appropriate metabolic tailoring of ART. Given the limitations in the use of statins, fibrates, and metformin during pregnancy, due to the pregnancy risk of these drugs, lifestyle intervention plays a pivotal role in the metabolic management of HIV-infected pregnant women.

There is no need to confirm, in the HIV setting, the beneficial role of stopping smoking and substance use programs and of dietary intervention for the health of both mother and child. Specific advice and dietary counseling, such as "Eating while you are pregnant" from the Food Standards Agency, can be recommended to pregnant women[40,41]. Recently, a summary of the work accomplished at a workshop sponsored by the National Institute of Health to review the existing evidence to support changes in the recommendations regarding nutrient requirements for people living with HIV and AIDS, including for pregnant women, has been published[42].

Current Food Standards Agency advice is to consume two portions of fish a week, one of which should be oily. No more than two portions of oily fish should be consumed.

A 10 µg vitamin D supplement is required as this level is not usually achievable through diet. It is especially important for those most exposed to deficiency risk[43]:

- women from South Asian, African, Caribbean or Middle Eastern family origin
- women who have limited exposure to sunlight (i.e. housebound or women usually remaining covered when outdoors)
- women eating a diet particularly low in vitamin D
- women with a pre-pregnancy BMI > 30.

Metabolic tailoring of antiretroviral therapy in pregnant women

Several retrospective and prospective cohort studies, administrative and clinical databases, and randomized controlled trials have assessed the direct contribution of ART (drug classes or specific antiretrovirals) to the risk of metabolic disorders and cardiovascular diseases. The same information cannot be directly applied to pregnant women, since we have to consider eventual teratogenicity and physiological changes of lipid and glucose metabolism previously described. Nevertheless, it is unlikely that the metabolic derangement observed in non-pregnant

HIV-infected individuals may have a weaker impact, but rather worsen the metabolic profile of pregnant women.

We have previously quoted a few studies that analyze the impact of ART drug classes on lipid and glucose abnormalities that appear to magnify the expected metabolic changes observed in the general population. In the absence of specific trials that compare head-to-head single drug regimens and classes, new data are rather represented by a greater reassuring message provided by the DHHS guidelines regarding the use of tenofovir, atazanavir, and nevirapine during pregnancy[1]. These were confirmed by a recently published meta-analysis of clinical experience of efavirenz and by a paper on tenofovir during pregnancy.

Tenofovir (TDF) use in monkeys, at doses approximately twofold higher than that for human therapeutic use, shows decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy[44]. Clinical studies in humans (particularly children) show bone demineralization with chronic use, but the clinical significance is unknown and the drug appears not to be contraindicated during pregnancy[45,46]. A multicenter, observational, cross-sectional cohort study evaluated growth patterns and bone health in 68 TDF-exposed HIV-uninfected children born to HIV-infected mothers. It found that the exposure to TDF during pregnancy does not impair growth patterns and bone metabolism[47]. The findings reported by Siberry, et al.[5] from the multisite, US-based Pediatric HIV/AIDS Cohort Study (PHACS) are reassuring about the safety of TDF during pregnancy. Among over 2,000 births to HIV-infected women, all of whom received combination ART during pregnancy, those uninfected infants whose mothers received TDF as part of their regimen (median duration 4.8 months) were at no greater risk of low birth weight, low birth length, small head circumference, or reduced weight for gestational age than those not exposed. Remarkably, TDF use more than doubled in the last five years in this US-based cohort, and 43% of pregnant HIV-infected women in 2010 were treated using a TDF-based combination regimen.

Nevirapine (NVP) has been extensively used during pregnancy, especially in developing countries. In the recent past, NVP has been discouraged in pregnancy due to increased risk of symptomatic, often rash-associated and potentially fatal, liver toxicity among women with CD4 cell counts > 250 mm^3 when first initiating therapy[48,49]. It is still unclear if pregnancy increases hepatotoxicity risk. Current guidelines suggest that women who become pregnant while receiving NVP-containing regimens and who are tolerating the regimen well can continue with the therapy regardless of CD4 count[1]. The expected metabolic benefit provided by NVP, inducing a significant increase in high-density lipoprotein cholesterol levels, has been specifically shown to be present in HIV-infected pregnant women[50].

Atazanavir (ATV) is considered the most "metabolic friendly" PI. Several studies, both in naive and experienced patients, have shown its limited lipid impact and its neutral effect on glucose metabolism. Nevertheless, in the past this PI was discouraged during pregnancy due to a theoretical concern regarding increased indirect bilirubin levels, causing significant exacerbation in physiologic hyperbilirubinemia in newborns, but this has not been observed in clinical trials to date[51,52]. Transplacental passage is low, with cord blood concentration averaging 10-19% of the maternal delivery ATV concentration[51,52]. Two out of three intensive pharmacokinetics studies of ATV with ritonavir boosting during pregnancy and the pharmacokinetics study described in the recently approved product label suggest that standard dosing results in decreased plasma concentrations compared with non-pregnant adults[51,52]. However, for most pregnant women (not on interacting concomitant medications), no dose adjustment was needed. Atazanavir concentrations further reduced by ~25% with concomitant TDF use[51]. A study of 41 pregnant women described in the package insert for Reyataz© concluded that no dose adjustment of ATV was needed for the majority of pregnant women infected with strains of HIV susceptible to ATV. The exception was in ART-experienced pregnant women on either TDF or H2-receptor blocker (not both) who should receive an increase in ATV dose to 400 mg (with ritonavir 100 mg).

It is unclear whether pregnancy increases the risk of hyperglycemia, new onset or exacerbation of DM, and diabetic ketoacidosis reported with PI use.

Martinez, et al. have shown, in HIV-infected non-pregnant individuals with metabolic abnormalities associated to potent antiretroviral regimens containing PI, the potential benefit of switching from boosted PI to nonnucleoside reverse transcriptase inhibitors (NNRTI)[53]. These trials have not been conducted so far in HIV-infected pregnant women. Nevertheless, some experts suggest switching from lopinavir to

Table 2. Most commonly used antiretroviral drugs in pregnant HIV-infected women: toxicity data in human pregnancy and recommendations for use in pregnancy

ARV drug	Recommendations for use in pregnancy	Metabolic issue in the mother and/or in the foetus	FDA pregnancy class
Lamivudine + Zidovudine	Recommended	Increased risk of maternal anaemia	C
Abacavir	Alternative	–	C
Emtricitabine	Alternative	–	B
Tenofovir	Alternative. Preferred in chronic HBV infection	Foetus: no evidence of impaired growth patterns; no evidence of bone metabolism toxicity	B
Nevirapine	Preferred	Beneficial increased of HDL cholesterol. Switch from PIs in case of glucose metabolism alterations	B
Efavirenz	Use in special circumstances	Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of EFV	D
Atazanavir	Preferred	No evidence of significant exacerbation in physiologic hyperbilirubinemia in neonates Increased dose to 400 + RTV if on tenofovir or H2receptor blocking	B
Lopinavir	Preferred	May impaired insulin-resistant status of pregnant women	C
Darunavir	Alternative	–	*
Raltegravir	Use in special circumstances	Usefull if a rapid decrease of viral load is needed	*

Key to Abbreviations: ARV = antiretroviral, FDA = Food and Drug Administration, ABC= abacrvir; 3TC= lamivudine, FTC= emtricitabine, HBV = hepatitis B virus, NVP= nevirapine, EFV= efavirenz, RTV= ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI= nucleoside/nucleotide reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic; HDL= high density lipoprotein, H2= histamine 2.
*Insufficient data to assess for teratogenicity in humans.
Modified from NIH Guidelines[1].

ATV/darunavir[1,54] or from PIs to NNRTIs in women developing diabetes mellitus.

In the general HIV population, two drugs have been shown to be metabolically neutral: raltegravir and maraviroc.

Raltegravir (RAL) pharmacokinetics was investigated in a study presented at ICAAC 2010[55]. High neonatal concentrations of RAL were found following transplacental transfer in HIV-1-positive pregnant women[56]. Consistent with previous reports, RAL pharmacokinetics showed extensive variability. Raltegravir readily crossed the placenta. Raltegravir exposure was not consistently altered during the third trimester compared to postpartum and historical data, and the standard dose appears appropriate during pregnancy[57].

Maraviroc (MRV) is categorized as pregnancy B risk. The incidence of fetal malformation was not increased in embryo-fetal toxicity studies performed with MRV in rats at exposure area under the curve (AUC) approximately 20-times higher than human exposure. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, MRV should be used in human pregnancy only if clearly needed[1]. Preliminary studies on monkeys showed that a single intrapartum dosage of MRV resulted in a low fetal MRV concentration[58].

Evidence of the risk of birth defects with efavirenz use is limited. Ford, et al. recently updated in an AIDS journal a meta-analysis of birth defects in infants with first trimester efavirenz exposure up to July 2011[6]. In 21 studies, there were 39 defects among live births in 1,437 women receiving first trimester efavirenz (2.0%; 95% CI: 0.82-3.18). The relative risk of defects

comparing women on efavirenz-based (1,290 live births) and non-efavirenz-based regimens (8,122 live births) was 0.85 (95% CI: 0.61-1.20).

Table 2 shows the most commonly used antiretroviral drugs in pregnant HIV-infected women with toxicity data as well as recommendations for use in pregnancy.

Conclusions

Pregnancy itself contributes to metabolic derangements during pregnancy; pregnancy is a transitory state in the metabolic syndrome.

Close monitoring is needed to diagnose metabolic alterations that can lead to adverse outcomes in the mother, in the newborn, and potentially in adulthood.

A metabolically tailored management of ART must be considered.

Drug safety (with particular regard to new ART) in pregnant women must account for metabolic abnormalities and its impact at organ level as well as for tocolytic activity and teratogenicity.

Lifestyle interventions and an appropriate metabolic tailoring of ART drugs need to be considered in the prevention and treatment of metabolic alteration during pregnancy.

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