17th World Congress in Fetal Medicine

Prenatal assessment of fetal subcutaneous fatty tissue area with 3D USG techniques in children of HIV-positive mothers receiving antiretroviral therapy

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Objective

For adequate in-utero development to occur, the various factors that affect human fetal growth must act synergistically to enable newborns to reach their genetic growth potential and attain what is considered to be "normal" weight and body composition (balance of lean mass and fatty mass). Alterations in growth and body composition affect perinatal morbidity and mortality and pathological processes that continue well beyond the neonatal period. Some authors have even found a direct relationship between such alterations and the presentation of certain degenerative chronic illnesses in adulthood, such as hypertension, diabetes, metabolic syndrome (MS), and cardiovascular disease (1). In 1997, Bernstein described a prenatal two-dimensional (2D) ultrasound technique to measure subcutaneous fatty tissue in the arm and thigh, by manually selecting the axial planes of the bone to assess fetal body composition and demonstrate differences between accumulated fatty and lean tissues during the second half of gestation (2). In 2017, Borboa, Guzman and cols conducted a study to measure subcutaneous fatty tissue, in which they proposed and standardized the use of 3D ultrasound volume acquisition coupled with offline analysis using tomographic ultrasound imaging (TUI). To evaluate this technique's reproducibility, three expert ultrasound technicians examined 15 patients three times each. They obtained 13 axial planes and selected the three that showed higher intraclass correlation coefficients (ICCs) for the arm and thigh. Then, they determined which of the fatty and lean mass measurements of the humeral and femoral axial planes had better agreement and found that the tomographic planes with the best correlation and reproducibility were the union of the proximal third with the two distal, the middle of the bone, and the union of the proximal two-thirds with the distal (intra-class and intra- and inter-observer correlation coefficients > 0. 9) (3). Human immunodeficiency virus (HIV) infection is very serious during pregnancy because of its frequency and the complications that it can produce for the mother and fetus. Although the use of highly active antiretroviral therapy (HAART) has decreased the mother-to-child transmission rate of the virus to less than 2%, this aggressive treatment can be harmful to both the mother and the fetus and can lead to short-, medium-, and long-term complications (4). Six or more months of HAART treatment in children, adolescents, and adults has been associated with alterations in body composition, such as loss of fatty tissue, the redistribution of fatty mass, and changes in glucose and lipid metabolism (5). Although HAART treatment is necessary for pregnant women with HIV, in order to decrease the transmission of the virus from mother to child, it is known to have some side effects. One such effect is the redistribution of fat, which is known as HIV-associated lipodystrophy syndrome and is characterized by morphological alterations caused by heterogeneous changes in fatty tissue and, thus, body fat redistribution. This may or may not be associated with metabolic alterations. The most common morphological changes in fatty tissue are lipohypertrophy (i. e., the accumulation of fat in the abdominal area), lipoatrophy (i. e., the loss of fat in peripheral regions), and mixed lipodystrophy (i. e., a combination of lipoatrophy and lipohypertrophy) (6). Complications from metabolic and morphological alterations not only have aesthetic consequences, but may also increase the risk of cardiovascular and pancreatic diseases. Among people living with HIV/acquired immune deficiency syndrome (AIDS) who are treated with HAART, the prevalence of MS is high, ranging from 11. 2% to 45. 4% (6). Antiretroviral drugs are transported by the placenta during pregnancy and can reach concentrations as high as 50% of those detected in maternal blood. Therefore, the side effects that occur in postnatal life may also occur in the fetus because it has been exposed to the same treatment. However, no prenatal studies have been performed to assess the effects of this treatment on fetal body composition or fatty tissue (7). The objective of this study was to use 3D ultrasound to evaluate the fatty tissue areas of the arms and legs of fetuses of HIV-positive (HIV+) mothers receiving antiretroviral therapy.

Methods

This study was performed from March 2016 to July 2017 at the fetal growth clinic of the Maternal and Fetal Medicine Department through its Research Unit (Unidad de Investigación en Medicina Materno Fetal [UNIMEF]) at the National Institute of Perinatology (Instituto Nacional de Perinatologia [INPer]). A total of 34 pregnant patients of 36. 0–36. 6 weeks of gestation participated. Gestational age was determined based on the day of last menstruation and was corroborated with early ultrasonography (USG) (i. e., before 20 weeks of gestation). Seventeen patients were HIV+ and receiving antiretroviral treatment, and 17 were paired controls. All of the participating HIV+ patients had started HAART prior to pregnancy, and their treatment was not modified during pregnancy, because the disease was well controlled based on their viral loads and leukocyte counts. Before inclusion in the study, the patients were invited to participate, and the risks and benefits of participation were explained to them. Signed informed consent was obtained. Patients with diagnoses of chronic or pregnancy-induced hypertension or diabetes or whose fetuses had growth abnormalities were not included. The ultrasound assessment was performed using Voluson 730 Expert and Voluson E8 (General Electric Healthcare ®) equipment with a volumetric transducer (4–8 MHz). Fetometry (biparietal diameter [BPD], occipitofrontal diameter [OFD], abdominal diameter [AD], and femur length [FL]) was evaluated to calculate the fetal weight using the Hadlock 2 formula. Lean and fatty tissues in the extremities were evaluated based on sagittal planes of the arm and thigh using predetermined settings for 3D evaluation in the second and third trimester. The contrast and zoom were adjusted so that the structure filled 70–80% of the screen. The focus was adjusted at the zone of interest, which was located at the center, and the gain was adjusted to optimize the image. The 3D volume was obtained with a sweep angle of 30º and an acquisition time of 10 s. The arm and thigh closest to the mother's abdominal wall were selected, and the transducer was placed as close as possible to the extremity without applying pressure while there was no movement of the fetus or mother. The volumes acquired were evaluated via offline analysis using the General Electric ViewPoint 4D view to delineate the contours of the lean and fatty mass. TUI was programmed with 13 tomographic planes of the femur and humerus, with the shaft centered to obtain six right and six left planes, dividing the bone into equal distances. Only the three planes that had previously been selected were evaluated. Fatty subcutaneous tissue was measured by taking the total area obtained in this image and subtracting the center area corresponding to lean mass, which consists of bone and muscle. At least two measurements were taken of each tomographic plane, and the average value of each set of observations was used for the analysis. Three humerus/femur planes were analyzed: the union of the proximal third with the two distal, the middle of the bone, and the union of the distal third with the two proximal(Figure 1). The acquisition of images and offline analyses were conducted by three ultrasound experts (maternal fetal medicine specialists) who had participated in the standardization process. Statistical analysis was performed using SPSS, version 20 (IBM® SPSS® Statistics), and a descriptive analysis was conducted to characterize the population evaluated. The Mann-Whitney U and chi-square tests were used to evaluate differences. The protocol was implemented after acceptance and review by the research ethics committee of INPer.

Results

In total, 34 patients participated: 17 HIV+ patients receiving antiretroviral therapy and 17 controls with no pathologies that could affect fetal growth or body composition (e. g., hypertension, diabetes, obesity, or renal disease). The antiretroviral treatment scheme was established by the Department of Infectology, and all the participants began treatment before pregnancy. Of the 17 HIV+ patients, one (6%) received Lopinavir/Ritonavir, three (18%) received Lopinavir/Ritonavir+Tenofovir/Emtricitabina, and 13 (76%) received Lopinavir/Ritonavir+Lamivudina/Zidovudina. The viral load was evaluated upon conducting the ultrasound evaluation, and the findings for each of the 17 cases were "undetectable virus" and CD4 leukocyte count >500. The general characteristics of the population are shown in Table 1. No differences were found in maternal age groups (years), maternal weight (kgs), maternal size (mts), body mass index (BMI), parity (number of gestations), gestational age (weeks/days), fetal weight calculated in grams, or fetal gender proportion. The median values (in cm2) of the fatty subcutaneous tissue areas in the six planes selected (three humerus and three femur) were compared to evaluate differences between the groups studied (HIV+ vs. controls). For the femur, the median fatty mass area at the union of the proximal third with the two distal planes was 9. 22 cm2 (range, 5. 91–11. 42) for HIV+ cases vs. 11. 94 cm2 (8. 14–14. 34) for controls (p=0. 001). The median at the middle plane was 8. 22 cm2 (5. 91–11. 22) for HIV+ cases vs. 10. 14 cm2 (7. 88–13. 78) for controls (p=0. 003). The median at the union of the distal third with the proximal planes was 7. 84 cm2 (4. 91–11. 99) for HIV+ cases vs. 9. 50 cm2 (6. 43–13. 24) for controls (p=0. 004). For the humerus, the median of the fatty mass area at the union of the proximal third with the two distal planes was 5. 60 cm2 (range, 3. 4–7. 89) for HIV+ cases vs. 6. 84 cm2 (4. 32–11. 3) for controls (p=0. 048). The median at the middle plane was 5. 34 cm2 (3. 62–8. 15) for HIV + cases vs. 6. 26 cm2 (4. 64–12. 06) for controls (p=0. 018). Finally, the median at the union of the distal third with the proximal planes was 5. 10 cm2 (3. 34–7. 14) for HIV + cases vs. 6. 27 cm2 (4. 64–8. 87) for controls (p=0. 005). Differences were identified in the fatty tissue areas (in cm2), and statistical significance was found for the three tomographic planes from the femur and the three humerus measurements (Table 2, Figures 2 and 3). Of the HIV+ patients, 100% had caesarean sections (17/17), whereas 88% of the controls (15/17) had natural births. No obstetrical complications occurred in either group, and no perinatal complications were observed in any of the newborns.

Conclusion

Although we have determined that changes in the fatty tissue area result from antiretroviral treatment, it is important to mention that we are not suggesting that treatment should be suspended. Instead, we are highlighting the existence of other important factors that need to be considered, in addition to preventing the transmission of the virus. The findings of our study pave the way for implementing treatment schemes that do not produce alterations in the fetus, while being equally effective for preventing transmission. The results also suggest, that children of HIV+ mothers who receive antiretroviral treatment should be given a comprehensive evaluation during pregnancy, with medium- and long-term follow-up to determine the effects on growth and assess the metabolic alterations produced by this exposure in fetal life.