General Section

Placental and umbilical cord macroscopic changes associated with fetal and maternal events in the hypertensive disorders of pregnancy

A.K. Marques Salge[1], R. Maioni Xavier[1], W.S. Ramalho[1], É. Lopes Rocha[1], A.S.F. Coelho[1], J.V. Guimarães[1], K.M. Siqueira[1], D.R. Abdalla[2], M. Antoniazi Michelin[3], E.F.C. Murta[4]

[1]Nursing School, Goiás Federal University, Goiána, Goiás
[2]Oncology Research Institute (Instituto de Pesquisa em Oncologia - IPDN), Federal University of Triângulo Mineiro, Uberada, Minas Gerais; [3]Oncology Research Institute (Instituto de Pesquisa em Oncologia - IPDN) Immunology Department, Federal University of Triângulo Mineiro, Uberada, Minas Gerais; [4]Oncology Research Institute (Instituto de Pesquisa em Oncologia - IPDN) Obstetrics and Gynecology Deparment, Federal University Triângulo Mineiro, Uberada, Minas Gerais (Brazil)

Summary

Aim: The purpose of this study was to identify placental and umbilical cord macroscopic changes and correlate them to maternal and fetal clinical events in hypertensive disorders of pregnancy (HDP). *Materials and Methods:* The authors examined 150 placentas, 30 from each HDP group, totaling 120, and 30 from the control group. All placentas and umbilical cords were examined, recorded, and photographed. *Results:* The mean placental weight in the control group (526.3 ± 95.6 g) was greater than in the HDP (435.5 ± 43.1 g). Calciphylaxis was the most common macroscopic change found in the control and HDP groups in 27 (90%) and 118 cases (98.3%), respectively. *Discussion:* Pregnant women with HDP were relatively younger. In addition, due to low blood flow seen in HDP, the macroscopic changes found included lower placental weight, calciphylaxis in the maternal surface, and fibrin in the fetal surface. Because of all complications associated, most women with HDP had preterm infants who developed respiratory problems and had shorter umbilical cords.

Key words: Hypertensive; Newborn; Placenta; Pregnancy; Umbilical cord.

Introduction

A well-functioning placenta is crucial for fetal development and morphological changes found may indicate fetal and maternal clinical changes associated with intrauterine development [1].

Macroscopic examination of the placenta and umbilical cord can help determine fetal/neonatal prognosis. Placental weight, distance between the placental margins, and thickness and any macroscopic abnormalities are recorded. Further evaluation is required in the presence of some nonspecific abnormalities seen in diabetes, infections in the last trimester of gestation, and hypertensive disorders of pregnancy (HDP) [2].

Placental infarctions are common in the placenta of women with HDP. The maternal surface of the placenta is firm with a yellow-white appearance. Cone-shaped lesions measuring approximately 0.5 to one cm are seen in the decidua. They may be superficial or involve the entire thickness of the placenta [2].

The examination of the umbilical cord can provide valuable information on the progression of the pregnancy [3-5]. Abnormalities in any structure of the umbilical cord can indicate compromised fetal development, fetal anomalies, perinatal complications or even intrauterine fetal death [5].

Pathologic examination of the umbilical cord includes the measurement of its length and mean diameter. Umbilical cord site and type of insertion into the fetal surface of the placenta should be assessed, while taking note of the distance between the placental margin and insertion site, and color of the Wharton's jelly surrounding the umbilical blood vessels and their tortuosity. When present, focal pathological features including torsion, true knot, rupture, hematoma and constriction are recorded [2].

Hypertensive complications during pregnancy are the leading cause of maternal and fetal morbidity and mortality worldwide, occurring in about ten percent of all pregnancies. They are more common in nulliparous women, multiple gestations, women suffering from hypertension for more than four years, history of hypertension in a previous pregnancy, history of renal disease, and women with family history of preeclampsia [6].

Some potentially serious conditions are often associated with HDP, such as placental abruption, disseminated intravascular coagulation, cerebral hemorrhage, pulmonary edema, liver failure, and acute renal failure. Perinatal complications include: increased prematurity, intrauterine growth restriction, fetal distress, perinatal death due to intrauterine hypoxia, and increased risk in

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neonatal deaths. Maternal changes involve diffuse endothelial disruption associated with the development of circulatory disorders, while fetal changes involve hypoxemia and nutritional deprivation [7].

The main risk factors are mainly on the maternal side and include obesity, chronic hypertension, and genetic factors. Hypertension and proteinuria during the second half of pregnancy are key diagnostic criteria but clinical presentation, laboratory tests, and associated events may reflect a variety of disease manifestations [6].

To minimize the complications of HDP and reduce the high rates of maternal and perinatal morbidity and mortality, it is key to improve scientific knowledge through the study of placental and umbilical cord macroscopic changes. Research together with obstetric care enable to devise health actions and evaluate care quality for the prevention, promotion, and rehabilitation of pregnant women and fetuses/newborns through strategies and specific protocols of obstetric, neonatal, and placental assessment [8]. In addition, further investigation of factors associated with placental changes of HDP can help elucidate the etiology and pathogenesis of gestational diseases and predict fetal/neonatal outcome.

The current study aimed to identify placental and umbilical cord macroscopic changes and correlate them to maternal and fetal clinical events in HDP.

Materials and Methods

A prospective study was conducted in a public maternity hospital which is a reference center for high-risk pregnancies, in the city of Goiânia, central-west Brazil, between August 2009 and July 2010. The study population consisted of pregnant women clinically-diagnosed with HDP and healthy women (control group) undergoing vaginal delivery or cesarean section with the outcome of live births, stillbirths, and fetal death during the study period.

Hypertension was defined as an increase in systolic blood pressure equal to or greater than 140 mm Hg or in diastolic pressure equal to or greater than 90 mm Hg in two separate measurements made no more than one week apart. This classification follows the criteria established in the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy [9]. Preeclampsia occurs beyond 20 weeks of gestation and is characterized by high blood pressure accompanied by proteinuria (protein ≥ 0.3 g in 24-hour urine collection). In the absence of proteinuria, preeclampsia is suspected when high blood pressure is accompanied by signs and symptoms including headache, blurred vision, epigastric pain, abnormal laboratory test results, specifically low platelet counts (platelets ≤ 100,000 mm^3) and abnormal liver enzymes (increased aspartate aminotransferase or alanine aminnotransferase).

Pregnant women who had autoimmune diseases or other diseases that could lead to immunological changes, and those who received corticosteroid therapy during labor were exclued from this study. The control group comprised of pregnant women with no maternal complications during pregnancy, normal laboratory tests, and clinically normal newborns.

The authors evaluated all macroscopic changes on the fetal and maternal surfaces of the placenta and umbilical cord. All lesions were examined, recorded, and photographed.

Data was collected from medical records and transcribed into study forms. Collected information included socio-demographic variables (age, birthplace, level of education, occupation, and household income), underlying conditions, obstetric history, potential neonatal/fetal and maternal obstetric complications, neonatal anthropometric measurements, 1- and 5-minute Apgar scores, laboratory tests for evaluation of HDP, parity, and gestational age which was determined by the date of the last menstrual period, first-trimester ultrasound examination, and Capurro method. When gestational age assessment results were inconsistent, the results of the Capurro method [10] were used. Maternal underlying conditions were grouped according to the 10th Revision of International Statistical Classification of Diseases and Related Health Problems (ICD-10) [11] criteria; neonatal/fetal underlying conditions were grouped following Cartlidge and Stewart criteria [12].

Statistical analyses were performed with the use of SigmaStat® version 2.0. An electronic spreadsheet was created. Quantitative data were summarized using frequency distributions, means, and standard deviations. Parametric and non-parametric tests were used to assess associations identified in the statistical analysis.

The study project was approved by the Animal and Human Research Ethics Committee of Clinics Hospital of Goiás University (protocol number 101/2008). The research study followed all the recommendations of National Health Council Resolution 196/96 in Brazil, which provides guidelines and regulations for human research.

Results

The authors examined a total of 150 placentas: 30 placentas from each HDP group, totaling 120 and 30 placentas from the control group. All placentas were obtained from childbirths taking place at the public reference center for high-risk pregnancies in Goiânia (Brazil) between August 2009 and July 2010.

The mean maternal and gestational age in the HDP groups are shown in Table 1. The preeclamptic group had lower mean maternal age while the eclamptic group showed lower mean gestational age. The rate of premature birth (less than 38 weeks of gestation) was higher in the HDP group (42 cases, 35%), whereas four premature births (13.33%) were seen in the control group. No statistically significant difference regarding the rate of premature births was seen in the different HDP groups (Table 1).

Table 2 shows macroscopic placental measures. The mean placental weight in the control group was greater than in the HDP group. The maximal placental diameter and the lesser placental diameter were greater in the control group compared to the other groups. There was no statistically significant difference in lesser diameter, maximal diameter, and umbilical cord thickness between the groups studied. The mean cord thickness was greater in the control compared to the HDP group (Table 2).

Paracentral insertion of the umbilical cord was most common in the control group (27 cases, 90%). In the HDP group, paracentral insertion was also most common (87 cases, 72.5%), followed by central (16 cases, 13.3%), marginal (ten cases, 8.33%), and velamentous (seven cases, 5.83%).

Table 1. — *Mean maternal and gestational age in the preeclamptic group evaluated in a public reference center for high-risk pregnancies in Goiânia, Brazil from August 2009 to July 2010.*

HDP group	X ± SD of maternal age (years)	X ± SD of gestational age (weeks)
Control group	23.8 ± 1.9	39.5 ± 1.2
Chronic hypertension	22.3 ± 2.1	38.7 ± 0.8
Gestational hypertension	22.6 ± 1.8	38.1 ± 1.1
Preeclampsia	21.9 ± 1.2*	37.8 ± 0.9
Eclampsia	22.1 ± 1.7	36.7 ± 1.8 **

X ± SD mean ± standard deviation; * H = 12.455; $p < 0.001$; ** H = 9.807; $p < 0.001$.

Table 2. — *Mean placental measures in control and HDP groups evaluated in a public reference center for high-risk pregnancies in Goiânia, Brazil from August 2009 to July 2010.*

Mean placental measures ± standard deviation (X ± SD)	Control group (X ± SD)	HDP group (X ± SD)
Mean weight of placenta ± SD (g)	526.3 ± 95.6	435.5 ± 43.1*
Mean maximal placental diameter ± SD (cm)	20.2 ± 0.8	18.5 ± 1.2
Mean lesser placental diameter ± SD (cm)	17.5 ± 2.4	12.0 ± 1.2
Mean thickness of umbilical cord ± SD (cm)	1.5 ± 0.2	1.1 ± 0.4**
Mean length of umbilical cord ± SD (cm)	33.6 ± 0.9	31.8 ± 0.7

cm: centimeters; HDP: hypertensive disorders of pregnancy; SD: standard deviation; g: grams; X: mean; * H = 9.112; $p < 0.001$; ** H = 7.118; $p < 0.001$.

Table 3. — *Anthropometric parameters and 1- and 5-minute Apgar scores of newborns of mothers in the control and HDP groups evaluated in a public reference center for high-risk pregnancies in Goiânia, Brazil from August 2009 to July 2010.*

Anthropometric parameters	Control group X ± SD	HDP group X ± SD
Head circumference (cm)	33.5 ± 0.4	33.3 ± 0.1
Chest circumference (cm)	31.9 ± 0.5	31.8 ± 0.1
Weight (g)	2.889.3 ± 12.54	2.816 ± 16.71
Length (cm)	50.1 ± 0.8	49.5 ± 0.5
1-min Apgar score	7.1 ± 1.2	7.4 ± 0.9
5-min Apgar score	8.8 ± 0.3	8.8 ± 0.7

cm: centimeters; SD: standard deviation; g: gram; min: minute; X: mean.

True knots of the umbilical cord were not distinguished in the groups examined. Four (13.33%) false knots were found in the control group and 32 (26.66%) in the HDP group.

Calciphylaxis was the most common macroscopic change found in the control and HDP groups in 27 (90%) and 118 cases (98.3%), respectively. Placental infarction was seen in only one case (0.8%) diagnosed with eclampsia in the HDP group. Fibrin in the fetal surface of the placenta was identified in 65 cases (54.1%) and 18 (60%) in the HDP and control groups, respectively.

The mean placental weight was lower among calciphylaxis cases compared to the HDP group without macroscopic changes, 412.2 ± 37.1 g vs. 435.5 ± 43.1 g.

There was a statistically significant association between the presence of fibrin in the fetal surface of the placenta and length of the umbilical cord. HDP cases with greater fibrin (34 cases) also showed changes in the length of the cord (H = 10.426, $p < 0.001$).

Among fetal/neonatal conditions associated with HDP, the most frequent one was respiratory disorders (76 cases, 63.33%), followed by malformations (16 cases, 13.33%). There was a statistically significant difference in the occurrence of respiratory disorders in newborns of pregnant women with hypertension in all groups (H = 11.233, $p < 0.001$).

Regarding anthropometric parameters of newborns, there was no statistically significant difference in the 1-minute Apgar score in both control and HDP groups, as well as in other measures including birth weight, length, 5-minute Apgar score, and head and chest circumferences (Table 3).

Discussion

HDP are disorders specific to pregnancy and postpartum period that mainly affect primiparous women at extremes of reproductive life. This was corroborated by the study results for gestational age. Women in the control group delivered at 39.5 ± 1.2 weeks of gestation while those in the HDP group, especially eclamptic cases, delivered at 36.7 ± 1.8 weeks, of which 35% were premature newborns.

Several studies have investigated the relationship between placental changes, maternal age, and HDP [13-15]. The authors found that the mean age of normotensive patients was higher than HDP patients. In the Bazaga *et al.* study [16], the patients with chronic hypertension and preeclampsia had a statistically higher maternal age than non-hypertensive patients and lower maternal age (lower than 20) was seen in preeclamptic patients. The result of the present study corroborates with this finding as preeclamptic cases had a mean age of 21.9 ± 1.2 years.

The current study found a mean placental weight of 526.3 ± 95.6 g in the control group and 435.5 ± 43.1 g in the HDP group, with a statistically significant difference ($p < 0.001$). In a study conducted by Artico *et al.* [15], placentas of hypertensive and control patients had a mean weight of 461.1 and 572.1 g, respectively. Lower placental weight was positively-associated with small-for-gestational-age (SGA) newborns with mean placental weight of 402 ± 67.2 g, median 392.5 g [17].

Several factors including HDP can affect placental development and cause a low-weight placenta. This is explained by the fact that maternal hypertension may cause decreased placental blood flow, reducing the transfer of specific nutrients, such as glucose and amino acids, and may result in low fetal and placental weight [18].

There was no statistically significant difference between mean 1- and 5-minute Apgar scores in both groups, although 1-min Apgar score was lower in the HDP than in the control group. These data are in contrast to those reported in the literature. Placentas with changes consistent with low blood flow were associated with newborns with lower 1- and 5-minute Apgar scores. Low blood flow may have caused fetal harm with manifesta-

tions at birth such as low scores [19]. In addition, the lowest gestational ages, birth weights, and 1-minute Apgar scores were seen among patients with HDP [20].

HDP increase the risk of unfavorable perinatal outcomes, SGA, low 1- and 5-minute Apgar scores, neonatal infection, meconium aspiration syndrome (MAS), infant respiratory distress syndrome (IRDS), prematurity, hyaline membrane disease (HMD), and perinatal death [13].

Calciphylaxis was the most common placental macroscopic change found in both the control and HDP group, 90% and 98.3% respectively. There is an association between calcification and premature placenta (grade 3) in HDP. The most common change seen in grade 3 placenta in hypertensive pregnant women is early calcification with placental insufficiency and no physiological maturity. It has also been reported the association between grade 3 placenta in preterm fetuses and perinatal complications in 78% of cases, mainly related to pregnancy-induced hypertension (PIH), among others. Premature placenta is associated with increased rates of fetal distress, presence of meconium in the amniotic fluid, low Apgar scores, low birth weight, perinatal death, and consequently respiratory distress [13].

There is a relationship between placental infarction and PIH. In the present study, areas of infarction were detected in the placenta of one patient in the HDP group (0.8% of cases) who was diagnosed with eclampsia. Fibrin in the fetal surface of the placenta was found in 54.1% of cases with HDP and 60% in the control group. Hypertension only, preeclampsia and eclampsia can cause similar placental macroscopic changes, and their severity bears a relationship with the severity of clinical signs, especially the duration and severity of hypertension [2, 21]. A similar study found macroscopic infarctions in 61% of the cases studied with an area greater than about 5% of placental tissue in 16% [15]. There were 43% of ischemic placental changes and 17% of infarction [22].

A full-term umbilical cord is quite variable measuring 40 to 70 cm in most cases; less than 35 cm is considered short and more than 80 cm is considered long [13]. All cords evaluated in the current study were less than 35 cm; however, the HDP group had even shorter cords, especially in patients with eclampsia with measures as low as 26.6 cm.

The factors associated with the development of the umbilical cord are still unknown. It is believed to be related to movement and tension exerted by the fetus. Thus, any condition that may cause restriction of the uterine cavity or fetal movements can lead to reduced tension on the cord and consequently reduced development [2].

A short umbilical cord does not necessarily indicate any harm to the newborn, although it may be suggestive of poor intrauterine fetal movement, but are often associated with fetal distress, neonatal asphyxia, birth defects, poor labor progression, placental abruption, cord rupture, intrafunicular hemorrhage, puerperal uterine inversion, and even fetal death [2].

Umbilical cord thickness is determined by the amount of Wharton's jelly varying from one to two cm [2]. The HDP group showed significantly lower measures, 1.1 ± 0.4 cm.

Comparative studies have shown that arteries of infants born to mothers who had preeclampsia had twice as much collagen, reduced elastin, and hyaluronate content, which is replaced by sulfated proteoglycans. The accumulation of collagen with simultaneous reduction in elastin content of umbilical cord arteries can decrease elasticity of arterial walls and decrease fetal blood flow. Wharton's jelly's ability to retain water and prevent compression of the vessels is also impaired [23, 24].

Pregnancies that progress with HDP are characterized by early maturation of the umbilical cord. There is an imbalance of its contents affecting the elasticity of Wharton's jelly, which helps protect against compression of the umbilical vessels and preserves umbilical blood flow, ensuring adequate nutrient supply to the fetus [5]. Studies have shown that an increase in umbilical cord thickness is an adequate surrogate indicator for assessing fetal growth and predicting intrauterine growth and perinatal outcome [5, 24].

The insertion of the umbilical cord in the placenta may be central, paracentral, marginal or velamentous. Abnormal insertions include marginal (also known as battledore placenta) and velamentous cord insertion (when the cord insets into the membranes of the placenta), a rare condition with great impact to the fetus. The authors found abnormal insertions in 14.16% of the HDP group. The asymmetrical insertion of the umbilical cord leads to inadequate vascular supply and thus decreased functional and metabolic efficiency of the placenta, which affects oxygen and nutrient transport through the vessels of the cord and results in SGA newborns [25].

The pathogenesis of these abnormal insertions of the umbilical cord is not well-understood but is often associated with placental disorders, single umbilical artery, fetal malformations, labor complications, low birth weight, prematurity, abortion, and perinatal asphyxia [2].

The false knots of the umbilical cord found in the HDP group included segments of folded and overlapped vessels due to their uneven growth and generally have no fetal impact [25].

Placental macroscopic examination is not routinely performed as part of clinical obstetric practice. Studies have shown that only placentas associated with major events including premature birth, 5-minute Apgar score ≤ 6, multiple pregnancies, suspected placental abruption, or any severe placental abnormality are sent for macroscopic and microscopic examination. Macroscopically-normal placentas without any clinical indications for examination are cold-stored for three days and are examined in the event of maternal and neonatal complications [1].

Several studies have stressed the importance of placental examination following birth [2, 24] as a way to detect changes that may have an impact on fetal/neonatal well-being and reduce fetal/neonatal complications caused by

HDP. A protocol for placental examination is required to improve the quality of care provided to newborns born to mothers with HDP.

Conclusion

Pregnant women with HDP were relatively younger. In addition, due to low blood flow seen in HDP, the macroscopic changes found included lower placental weight, calciphylaxis in the maternal surface of the placenta, and fibrin in the fetal surface of the placenta. Umbilical cords were shorter and thinner in the HDP group compared to the control group. Because of all complications associated, most women with HDP had preterm infants who developed respiratory problems and had shorter umbilical cords.

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Address reprint requests to:
E.F.C. MURTA, M.D.
Oncology Research Institute (Instituto de Pesquisa em Oncologia - IPON)
Discipline of Gynecology and Obstetrics,
Federal University of Triângulo Mineiro
Avenida Getulio Guaritá s/n
Bairro Abadia - Uberada, Minas Gerais
38025440 (Brazil)
e-mail: eddiemurta@mednet.com.br