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**Maternal Haematological Parameters and Placental and Umbilical Cord
Histopathology in Intrauterine Growth Restriction**

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Umbilical arteries • 2-dimensional Doppler ultrasound

Significance of the study

Our aim was to improve the 50% detection rate of ultrasonographic fetal biometry in the diagnosis of intra-uterine growth restriction (IUGR). This study shows that the correlation between placental volume and birthweight is strong, and that the umbilical artery lumen area is decreased in IUGR. Among the maternal blood parameters only the platelet count correlates with clinical findings. The evaluation of these data can make the diagnosis more accurate.

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Abstract

Objective: To investigate the placental and umbilical cord histopathology in IUGR, and their relation to second trimester maternal haematological parameters. **Materials and Methods:** Patients were selected for IUGR group based on estimated fetal weight below the 10th percentile. Patients were recruited in the control group randomly. Patients were followed up with ultrasound, and blood samples taken between the 20-24th gestational weeks. After delivery and formalin fixation, weight and volume of the placenta were recorded and histologic samples were processed. **Results:** Maternal platelet count strongly correlates with placental weight ($r = 0.766$). On the other hand, neonatal weight correlates with placental volume ($r = 0.572$) rather than with placental weight ($r = 0.469$). Umbilical arterial lumen crosssectional area correlates with birthweight ($r = 0.338$). **Conclusions:** Maternal haematological parameters do not seem to affect neonatal outcome. Our main findings are the correlation of maternal platelet count with placental weight, that the correlation of placental volume with birthweight is stronger than the correlation of placental weight with birthweight, and the correlation of umbilical artery lumen cross sectional area with neonatal weight. Mild histopathologic alterations might occur in normal pregnancies, however sufficient fetal nutrition can be maintained. This compensatory function of the placenta seems to be insufficient when two or more pathologies are present, which is characteristic for IUGR.

Introduction

Intrauterine growth restriction (IUGR) increases perinatal mortality by 10-25% and morbidity by 50-75% and predisposes the newborn to metabolic syndrome, diabetes mellitus, stroke and heart disease. The placental microvasculature is essential for the sufficient transfer of gases, nutrients and metabolites between the mother and the fetus [1]. The size, weight and shape of the placenta may vary within wide extreme values, and placental size is related to its ability to transfer nutrients [1-2]. The relationship between placental morphometry and adverse pregnancy outcome, including IUGR is known [3]. Small placental size, decreased placental surface area [4] and small placental volume [5] have been associated with increased risk of IUGR. Placental weight increases linearly as gestation progresses and its capacity to transfer metabolites increases and compensates for its slow growth related to fetal development. Weight and volume of placentas associated with IUGR are lower than that of their normal-weight counterparts [6]. Placental co-efficients (placental weight/fetal weight ratio) between 0.10 and 0.18 are considered normal. The literature is not consistent regarding overall placental volume. In some cases as the functioning placental tissue tries to compensate for the reduced circulation, the placental weight might not be reduced in IUGR [7]. Placentas of infants with IUGR are characterized by smaller diameters, increased placental coefficient and decreased placental weight and volume as compared to that of normal-weight infants [8]. It is not clear yet how placental weight and volume are related. Sonographically placental volume can be used to detect placental growth restriction that precedes fetal IUGR by several weeks [9]. There are placental vascular pathologies (calcification, reduced capillarization in the terminal villi, reduced cytotrophoblast proliferation, chronic villitis, infarcts, perivillous fibrin deposition, etc) that are associated with growth restriction, the presence of which does not explain how low birthweight and mild forms are present in normal pregnancies too [10].

Placental function can be assessed in vivo by utero-placental Doppler flow velocimetry, and fetal growth can be assessed by serial ultrasonic biometry. The flow velocity waveform in the umbilical artery normally shows low resistance in the last trimester of pregnancy, and this is thought

to reflect the development of the villous vascular tree [11]. High resistance in the umbilical artery is widely used as an indicator of placental dysfunction, where the elevation of resistance correlates with the maldevelopment of the tertiary villi [1]. Low for gestational age fetuses show abnormal blood flow velocity wave forms in the umbilical and uterine artery with reduced, absent or reverse diastolic flow and abnormally reduced blood flow per unit of fetal weight. IUGR remains a diagnostic challenge, as ultrasound provides a detection rate of only 50%. The explanation for low detection rate might be that biometry and flowmetry does not give direct information about the ratio of functional/pathological placental tissue, it provides information only indirectly [12].

Maternal hemoglobin level (Hgb) might be another marker in IUGR screening. High placental co-efficient with low maternal Hgb suggests differences of placental growth related to fetal growth [13]. Although severe anemia is associated with IUGR, maternal iron status cannot be assessed simply from Hgb concentration because plasma volume is increased in pregnancy and Hgb concentration decreases accordingly. The failure of the plasma volume to expand itself might cause growth restriction too [14]. Mean corpuscular volume (MCV) of red blood cells does not change substantially during pregnancy, therefore it might be a better choice for predicting adverse fetal outcome [14]. Yet there is no sufficient evidence of a relationship between placental ratio, Hgb concentration or MCV [15]. Other studies report that the decrease in haemoglobin concentration in pregnancy is related to birth weight; failure of the Hgb concentration to fall below 105 g/l indicates an increased risk of low birth weight and preterm delivery [16]. High blood viscosity, elevated platelet count (PLT) and spontaneous platelet aggregation can be a risk factor for vascular occlusions and a novel risk factor for adverse pregnancy outcomes such as pre-eclampsia and IUGR too [17]. Most studies on the inter-relationships between antenatal uteroplacental Doppler blood flow velocimetry and the postnatal findings have focused on the microscopic and ultrastructural characteristics of the placenta [18] or the relationship between fetal weight and the gross morphology of the placenta [19].

The objective of this study was to evaluate pathological changes of the placenta and umbilical cord in connection with IUGR pregnancies and to investigate whether birthweight or placental changes are influenced by maternal hematologic blood parameters.

Materials and Methods

Study Design

Pregnant subjects were recruited in a prospective case-control study between January 2014 and December 2016 in the Department of Obstetrics and Gynecology, University of Szeged, Szeged, Hungary. Each subject signed informed consent in accordance with the Declaration of Helsinki and were followed up until delivery. Clinical data were collected from the medical anamnesis, blood parameters were taken in the second trimester, between 24th-30th weeks of gestation. Subjects were classified into the IUGR group if the estimated fetal weight on the 20th week of gestation was below the 10th percentile as per race, gender and gestational age, and recruited into the control group randomly. For birth weight percentile we used the sex-specific percentile scale of the International Society of Ultrasound in Obstetrics and Gynecology [20]. Patients with twin pregnancies, preterm births, genetic malformations, chromosomal or developmental disorders, hypertension (<140/80 Hgmm), diabetes (fasting plasma glucose <6.9 mmol/l measured at 24th week of gestation), alcohol, nicotine or drug abuse were excluded from the study. Patients involved in the study did not have immunological, cardiovascular, gastrointestinal or pulmonary disease.

Data Collection

Every ultrasound examination was performed by the same person to avoid interobserver variability. All patients were scanned in a semirecumbent position. The factorial default setting "Obstetrics/2-3 trimester" was used in 2-D mode on a GE Voluson 730 machine. Gestational age was determined based on the first day of the last menstrual period and on ultrasound biometry (crown rump length and biparietal diameter) between 9-11th weeks of pregnancy. In the 20-24th week fetal biometry was used to assess estimated fetal weight by the formula B of Hadlock [21]. A conventional color Doppler study of the umbilical arteries were also performed and the S/D ratio was read from

report display of ultrasound. After delivery the weight of the neonate and placental volume were measured. For volume measurements we used the water replacement technique.

Umbilical Cord and Placental Sample Processing

After 3-7 days of formalin fixation, placental weight and volume were measured and gross examination of the placenta and the umbilical cord was executed by an expert pathologist according to the Guideline of Royal College of Pathologists, 2011 [22]. After measuring the diameters, the placenta was cut along the longest diameter in 1 cm thick strips using a brain knife and the thickness of the tissue was measured at the umbilical cord insertion. Umbilical cord samples were taken from the placental end and cut into transversal slices of four millimetres, perpendicular to the umbilical cord. The slices were dehydrated in graded ethanol series, cleaned in xylene and embedded in paraffin. Paraffin samples were sectioned at 4 micrometers. After Haematoxylin/Eosin (HE) staining histologic samples were analyzed via Axio Vision SE64 Rel. 4.9.1. microscope. The following parameters of the umbilical cord were measured in digitised HE stained sections; umbilical cord longest cross sectional diameter, vessel lumen area and vessel wall thickness. Because of the umbilical cord coiling, the surface of the vessels were not mathematically-perfect cross sections, and we standardized our measurements to the highest point of torsion, lowest point of torsion and an extra measurement at 3, 6 or 9' O clock position depending on the first two points. Placental histological samples (3mm x 10mm x 20mm) were taken from the umbilical cord insertion, the edge of the placenta, the fetal and maternal side of the placenta and from the pathological alteration(s), if there were any.

Statistical Analysis

For normally distributed maternal and neonatal characteristics and outcomes of the umbilical cord and placenta we used t-test, and Analysis of Variance (ANOVA) was applied to assess differences in vessel wall thickness depending on different lumen shapes in arteries. The Kruskal-Wallis test was applied to skewed variables with Bonferroni correction. Differences were considered statistically significant at $p < 0.05$. After a mutiparametric correlation analysis with post-hoc

adjustment for multiple comparisons, linear regression analysis was applied to investigate the relationships among maternal blood parameters and clinical outcome. Correlation was evaluated as “strong” if the value of r was above 0.5, “moderate” between 0.3 and 0.5 and “weak” under 0.3. All analyses were performed via Prism 6 (Graph Pad Software Inc. San Diego USA).

Results

54 patients (46 controls, 8 IUGR) were recruited. Clinical data and maternal blood parameters are shown in Table 1. Values of mean corpuscular volume of red blood cells ($r = 0.0487$), red blood cell count ($r = 0.0147$), hemoglobin ($r = 0.1098$), hematocrit ($r = 0.0016$), platelet count ($r = 0.0009$), prothrombin time ($r = 0.0048$), INR ($r = 0.0148$) or activated partial thromboplastin time ($r = 0.0240$) did not correlate with neonatal weight. Platelet count showed strong correlation with placental weight ($r = 0.7660$). Gross pathological examination revealed that placental volume measured right after delivery shows the strongest correlation with birthweight rather than with placental weight or with volume after formalin fixation (Fig. 1). The results of histological examination are shown in Tables 2 and 3. The prevalence of obliterated, star-shaped lumen in one or both arteries did not differ in the IUGR or control cases (Fig. 2), but the lumen-cross sectional area shows mild correlation with birthweight ($r = 0.336$). We found nonconversion of maternal arteries in the placenta that is similar to that of the uterine arteries seen via ultrasound as end diastolic stop of blood flow (notch). The five such cases did not coincide with notch in uterine arteries in our ultrasonographic data on uterine arteries.

Discussion

This study shows that the correlation between placental volume and birthweight is stronger than the correlation between placental weight and birthweight. The umbilical artery lumen area is significantly decreased in IUGR pregnancies. Among the maternal peripheral venous blood parameters only the platelet count correlates with the clinical findings. Other blood parameters that could alter maternal blood viscosity seem to have no effect on fetal weight. Blood samples were taken

between the 20th-24th weeks of gestation, right after when the placental vascular tree had developed and the ultrasonographically measurable signs of placental malperfusions were detectable.

The results draw attention to antenatally measurable possible predictor of intrauterine growth restriction, the placental volume, the shortest diameter of placenta and the lumen area of umbilical arteries in IUGR. The strength of this study is that each kind of measurement was performed blindly and by only one researcher. A limitation of this study is the small number of cases. In our clinic the annual birthrate is about 2300, and IUGR pregnancies with known etiologic backgrounds (other than placental insufficiency) were excluded.

Elevated numbers of maternal mononuclear cells and increased levels of cytokines have been reported in preeclampsia, and also the cytokine levels produced is higher. The high proinflammatory cytokine concentration may cause endothelial dysfunction and thus vasoconstrictions [23]. We excluded pregnant patients with preeclampsia or hypertension, and in connection with intrauterine growth restriction we did not observe the same correlation. Based on the data collected from maternal hemathologic parameters in our study, we would not suggest them for further studies of predictors of low birthweight. Only the platelet count shows correlation with clinical findings and it does not affect birthweight. In contrast with the cellular compounds of the maternal blood, cytokines and tumor necrosis factor alpha (TNF- α) levels might be worth measuring in IUGR pregnancies [23-24].

Our data shows that placental volume measured after delivery has stronger correlation with birthweight than does placental weight with birthweight. Although these parameters differ significantly between the two groups, they do not reflect functional variability within the tissue. In a large placental disc with confluent infarctions, calcification would still be in the upper range of weight and volume but would belong to a growth-restricted fetus. We recommend the development of a reliable in-utero method to estimate functional placental volume that refines the estimated fetal weight. We also suggest establishments of percentile curves of trimmed placental weights to be used for predicting growth restriction. The placental volume can be estimated by ultrasound more accurately than by placental weight [13]. Placental volume and shape also can be determined via

medical resonance imaging (MRI). MRI gives additive information about the textural features and shape of the placenta. Placentas in IUGR pregnancies tend to be more oval and thicker than placentas of healthy fetuses which are more circular [25]. Our morphologic measurements support these observations. Some studies managed to establish a percentile curve placental volume. After some routinely performable measurements, new diagnostic reference values could be used [26]. 3-dimensional placental measurements in the first trimester showed moderate correlation with fetal weight. Measurements in the second trimester performed along the fetal side of the placenta have better predictive values (up to 45%) and can be used for screening patients at high risk [27].

Our results confirm that mild histopathologic alterations might be present in normal pregnancies, until there is enough functional placental tissue, sufficient fetal nutrition can be maintained [13]. This compensatory residual of the placenta becomes insufficient when two or more pathologies are present, which is characteristic for IUGR. We have found nonconversion of the arteries in the maternal side of the placenta. The five cases did not coincide with notch in uterine arteries. With a mathematical model it has been demonstrated that the vessel wall shear stress and blood velocity jets are bigger in uterine arteries in IUGR and also vortices occur more often in the intervillous space [28]. This condition of increased turbulence with increased platelet count promotes the formation of microthrombus that explains the intervillous deposition of fibrin and increased placental weight related to birthweight in IUGR pregnancies. Umbilical vessels are coiling together along the cord and their cross section perpendicularly to the longitudinal axis of the cords will rarely be a true mathematical cross-section. This artefact causes torsion, oval or bean shaped lumen and variability in measurements of vessel wall thickness. In cases of strict arterial constriction, a star shaped lumen can be seen. To overcome this adversity we standardized our method based on this torsion and performed an additional measurement semi-independently. This method is reproducible in ultrasonography. Only the lumen cross-sectional area of the umbilical arteries differed between the IUGR and control group. Our finding of non-significantly decreased arterial vessel wall thickness conforms to published literature [29-30].

Conclusion

The novelty of our study is the correlation of maternal platelet count with placental weight, the stronger correlation of placental volume with birthweight than the correlation of placental weight with birthweight, and the correlation of umbilical artery lumen cross sectional area and neonatal weight. Larger studies are needed to ascertain whether these alterations in umbilical arteries are part of a fetal response to under-nutrition or the etiology of part of IUGR. Further studies are also needed to establish a diagnostic method involving similar findings to increase the accuracy of predicting fetal outcome.

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Table 1: Clinical data of the mothers and newborns

	IUGR (n = 8)		Control (n = 46)		<i>p</i>
	mean	±SD	mean	±SD	
MCV (fL)	84.48	0.96	88.25	1.26	ns
RBC (T/L)	4.07	0.03	4.03	0.10	ns
Hgb (g/L)	123.80	4.48	121.50	2.31	ns
Htk (L/L)	0.35	0.01	0.36	0.01	ns
PLT (Giga/L)	235.50	24.73	197.80	11.81	ns
MPV (fL)	10.65	0.66	12.01	0.32	ns
Prothrombin time (sec)	12.80	0.10	12.93	0.13	ns
INR	0.97	0.01	0.98	0.01	ns
APTT (sec)	33.93	0.26	32.03	0.47	ns
umbilical artery S/D	3.39	0.38	2.22	0.11	0.0006
maternal age (year)	29.75	1.11	25.72	3.64	ns
maternal BMI (kg/m ²)	28.48	2.35	22.46	1.83	ns
parity	0.85	0.16	1.48	0.34	ns
Birthweight (g)	2110.00	194.0	3367.73	435.04	0.0023
Gestational age (weeks)	37.29	1.10	38.58	1.58	ns
1' Apgar score	7.71	1.14	8.38	1.85	0.036
5' Apgar score	8.86	1.46	9.46	1.13	ns
10' Apgar score	9.57	1.13	9.92	0.28	ns
male (%)	50.00	-	45.94	-	ns
female (%)	50.00	-	54.05	-	ns

Maternal peripheral venous blood parameters: MCV = mean corpuscular volume of red blood cell, RBC = red blood cell count, Hgb = haemoglobin, Htk = hematocrit, PLT = platelet count, MPV = mean platelet volume, INR = international normalized ratio, APTT = activated partial thromboplastin time, BMI = body mass index. Arteria umbilicalis S/D = the systolic and diastolic blood flow velocity ratio, ns = not significant.

Table 2: Placental histopathologic alterations

	IUGR (n = 8)		Control (n = 46)	
	n	%	n	%
Focal calcification	2	25.00	5	10.87
Villous hypovascularization	4	50.00	2	4.35
Villous hypoplasia	4	50.00	7	15.22
Intervillous fibrin deposition	3	37.50	5	10.87
Syncytial nod	3	37.50	1	2.17
Amnion nodosum	0	0.00	1	2.17
Villitis	0	0.00	1	2.17
Haematoma	0	0.00	2	4.35
Nonconversion of maternal vessels	2	25.00	3	6.52

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Table 3: Umbilical cord and placental pathology

	IUGR (n = 8)		Control (n = 46)		<i>p</i>
	Mean	±SD	Mean	±SD	
Vena umbilicalis vessel wall thickness (µm)	663.8	41.6	605.4	20.6	ns
Vena umbilicalis lumen area (µm ²)	1563000.0	1054000.0	1803000.0	514365.0	ns
Arteria umbilicalis vessel wall thickness (µm)	636.4	41.0	678.2	15.0	ns
Arteria umbilicalis lumen area (µm ²)	146825.0	18369.0	526659.0	77690.0	0.0296
Ratio of star shaped arteries	0.71	0.29	0.89	0.13	ns
UCI	1.05	0.27	1.52	0.44	ns
Umbilical cord diameter (mm)	93.20	8.34	116.10	6.24	ns
Number of placental pathologies present	2.13	0.30	0.70	0.11	< 0.0001
Native placental volume (ml)	315.30	23.44	492.50	17.95	< 0.0001
Placental volume after formalin fixation (ml)	368.80	23.15	461.50	15.01	0.0018
Placental weight after formalin fixation (g)	401.80	18.33	468.90	15.49	0.0226
Longest placental diameter (cm)	15.50	1.15	15.86	0.20	ns
Shortest placental diameter (cm)	13.11	0.46	14.39	0.29	0.0196
Placental thickness (cm)	2.58	0.14	2.71	0.08	ns
Placental co-efficient	1.19	0.01	0.14	0.01	< 0.0001

Figure Legend

Fig. 1. Placental morphometry; placental volume measured after delivery (A) shows the strongest correlation with birthweight not the placental volume (B) or weight (C) after formalin fixation.

Fig. 2. Placental and umbilical cord histopathology; normal placental tissue (A) with vascularized villi and intrauterine growth-restricted placental tissue (B) with hypovascularization and intervillous fibrin deposition. (HE, 200x)

Different coiling patterns (C) that can distort vessel cross section and an obliterated, star shaped umbilical artery lumen (D) with perivascular haematoma and asymmetrical vessel wall. (HE, 400x)

Perivascular haematoma is the result of intrapartum pulling of the umbilical cord.

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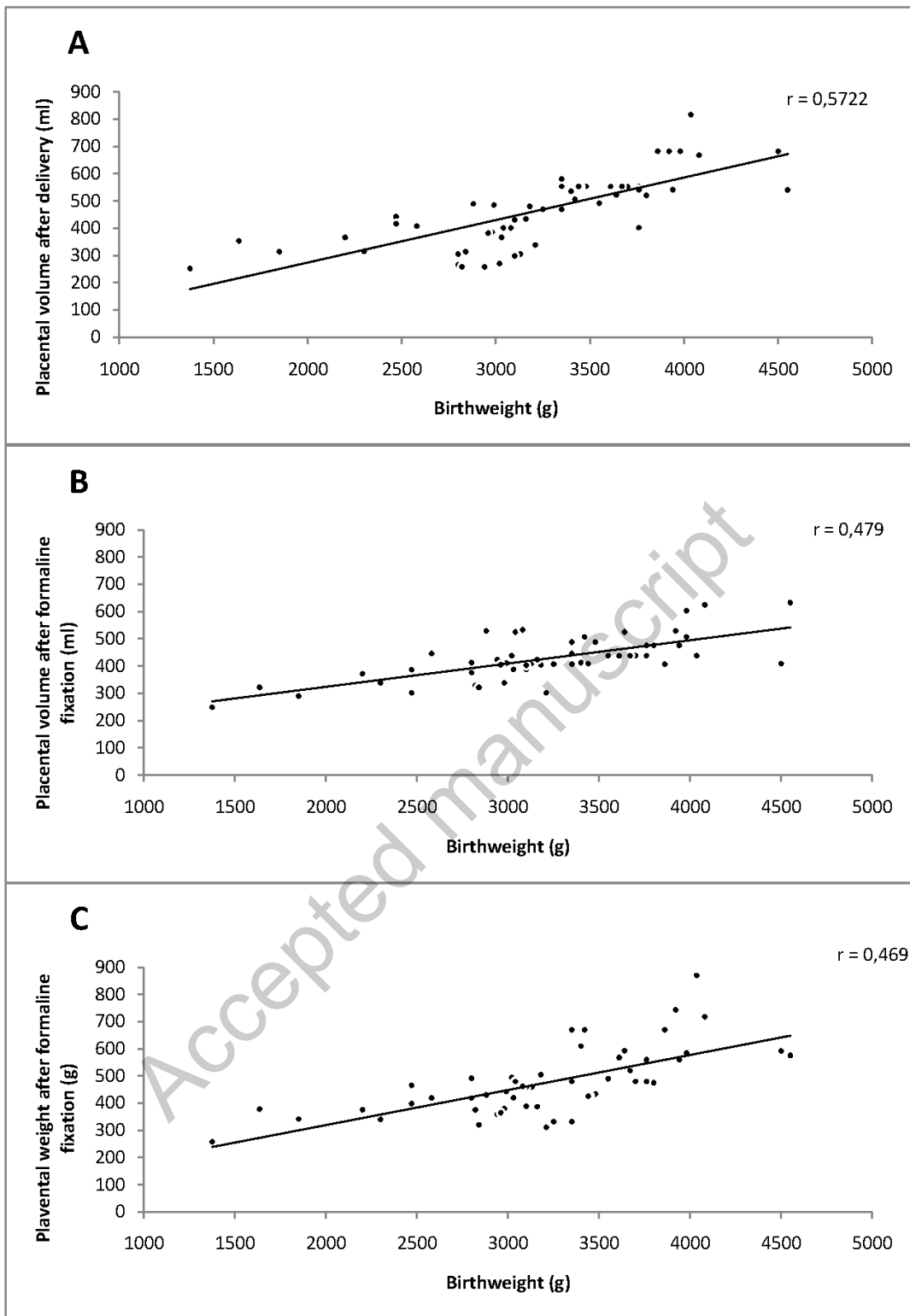


Fig. 1.

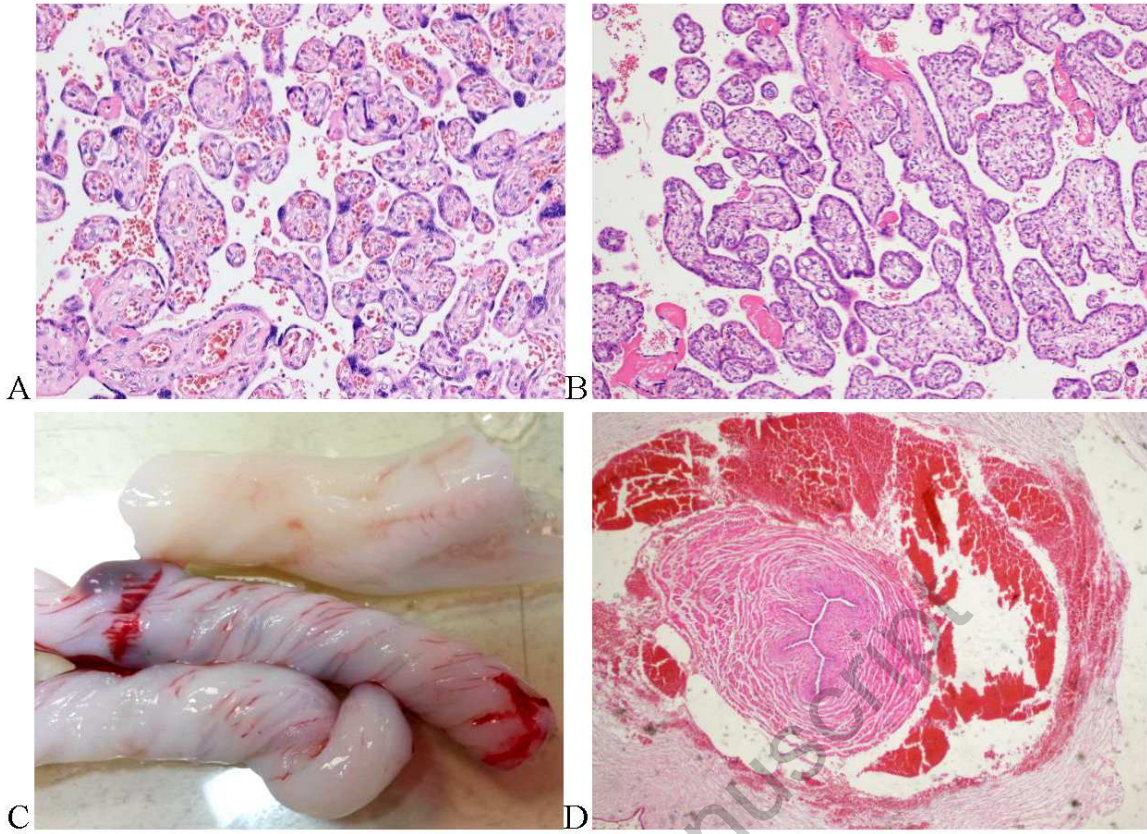


Fig. 2.