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Placental Growth during Normal Pregnancy – A Magnetic Resonance Imaging Study

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Key Words
Placenta · Obstetric · MRI · Pregnancy

Abstract
Objective: To investigate normal human placental growth longitudinally throughout the second and third trimesters using MRI. ***Methods:*** Twenty normal, first-time singleton pregnancies were scanned 7 times between the 14th and 38th week of gestation, at 4-week intervals, using MRI. Placental volumes were measured in both sagittal and transversal slices. All placentas were weighed after delivery to make a comparative study. ***Results:*** Sixteen of the 20 women had increasing placental volumes from the 14th to 38th week of gestation. The 6th and 7th scan showed that 4 women had placentas of the same size. The mean placental volume increases linearly from the 14th till the 38th week of gestation, with a constant mean growth rate of 29.97 ml/week. The median placental volume extrapolated to delivery was to 856 ml (range 602–1,050 ml). The median weight of the exsanguinated placenta after delivery was 640 g (range 500–787 g). All pregnancies were carried to term, resulting in the delivery of healthy infants with good correlation between placental size and birth weight (R = 0.56, p = 0.009). ***Conclusion:*** Placental growth was measured systematically in a longitudinal study through the second and third trimesters using MRI. MRI provides a safe and feasible method to measure placental growth. The mean placental growth was linear throughout the second and third trimesters.

Introduction

It is well known that fetal size at birth directly correlates with the placental growth [1–3]. The normal growth of the fetus depends on the normal growth of the placenta. MRI is considered a safe and feasible tool to measure the intrauterine growth of the placenta [4, 5]. No adverse effects were found in the follow-up studies of infants who underwent in utero MRI scans [6–8].

Ultrasound is used clinically throughout pregnancy to estimate fetal growth. However, by the end of weeks 16–18, the placental size exceeds the ultrasound field of view, and the placental size cannot be fully obtained. MRI provides images of the whole placenta throughout pregnancy with excellent soft tissue contrast, without the use of contrast agents or the need of sedation of the mother or the fetus.

Study carried out at Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

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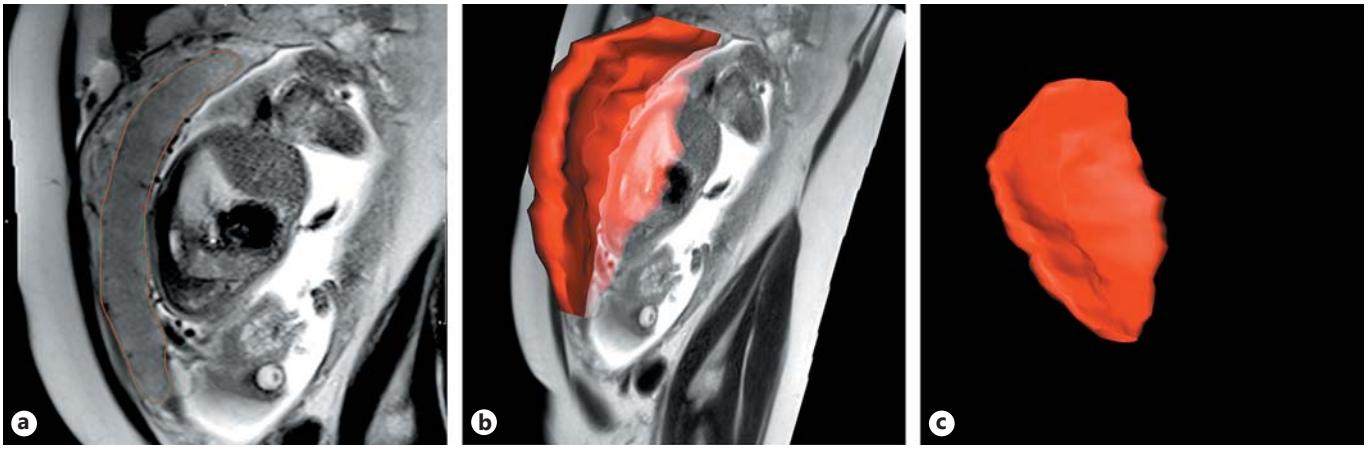

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Fig. 1. a Placenta and fetus in sagittal plane; **b**, **c** 3D model of placenta.

A few studies have been carried out using MRI to determine placental growth during pregnancy [1, 2, 9, 10]. These studies evaluated the growth of the placenta comparing infants with various diseases to infants with normal growth.

All previous studies have been restricted to second and third trimester trials, as the recommendations still advise against exposing the fetus to high-field MRI during organogenesis in the first trimester [11–14].

The aim of this study was to make a normogram of normal placental growth rate in the second and third trimesters, measured by MRI in a longitudinal, prospective study, with regular fixed 4-week intervals between scans.

Materials and Methods

This study was carried out in 21 singleton first-time pregnancies that underwent 7 MRI scans at 4-week intervals during the second and third trimesters. All volunteers were enrolled in the trial around the 12th week of gestation as the women attended a routine fetal first trimester ultrasound scan at the Department of Obstetrics, Copenhagen University Hospital, Denmark. Flyers with study information were placed in the Ultrasound Department. If the inclusion criteria were met, oral information about the trial was given by one of the physicians involved in the trial. Inclusion criteria were age between 18 and 40 years, body mass index between 18 and 30 kg/m^2 (before pregnancy), non-smokers (at the start of the study or having stopped 6 months prior to the start of pregnancy), participants should not previously have given birth or had a second trimester abortion, natural conception (without fertility treatment of any kind), singleton pregnancy and no vaginal bleeding during the first trimester.

Women with known diabetes, hypertension, cardiac disease, kidney disease, anemia or other medically treated diseases that could influence the pregnancy were excluded. Gestational age (GA) was calculated from the day of conception (determined by crown-rump length at the first trimester ultrasound scan). For body surface area (BSA), the Mosteller formula was used, which is feasible to determine BSA for this group of patients [15]. All participants gave oral and written informed consent before enrolment. The Danish Scientific Ethical Committee approved the study (file No. H-2-2011-0127).

Twenty three women were enrolled in the trial. Two women were excluded from the trial shortly after inclusion; one had failed to inform that she had received fertility treatment; one had failed to inform that she was using antidepressant medication. One woman developed pregnancy-related pelvic girdle pain and did not participate in the last 2 scans. All the other included subjects completed the study.

The same 1.5 Tesla MRI scanner (Magnetom Espree, Siemens Medical Solutions, Erlangen, Germany) was used for all MRI scans. A body coil was used for abdominal (uterus and placental) imaging. All women were placed in the MRI scanner in head first supine position, but tilted 20–30 degrees to the left, using customized cushions, in order to reduce compression on the inferior vena cava during the scans. Measurements of the uterus included localizer sequences in the transverse, sagittal and coronal planes.

Overall, the pregnant woman spent approximately 45 min under the scanner during each MRI session, which included a heart sequence as part of another trial in addition to the uterus trial, with a short break for body and coil reposition between each part of the session.

For uterus sagittal and transversal imaging, T2-weighted HASTE turbo spin echo sequences (free breathing; no slice gap; TE 92; TR 1,350; FOV 270–350 mm; slice thickness 7 mm) were used.

For measurement of placental size, software from Cvi42 was used (version 4.1.5, Circle Cardiovascular Imaging Inc., Calgary, Alta., Canada). The software is designed for cardiac analysis, but it proved to be well suited even for conducting the volumetrical analysis of the placenta. MRI provides high tissue contrast, which (in most cases) makes placental border easily identified. A 3D model of the placenta was generated as a control tool, which was used to validate the borders of the placenta in the sagittal and transversal slices (fig. 1). Placental volume was cal-

Table 1. Placental volume and placental weight in second and third trimesters

Scan number	GA median, weeks (weeks + days)	GA range, weeks + days	Mean placental volume, ml (median)	Placental volume range, ml
1	13.7 (13+5)	13+1 – 14+5	85.1 (79.5)	53.0–149.0
2	17.6 (17+4)	16+0 – 18+6	175.3 (170.3)	115.5–322.0
3	21.9 (21+6)	21+1 – 22+5	292.0 (297.5)	209.0–422.0
4	26.1 (26+1)	21+1 – 27+5	432.7 (409)	323.0–577.0
5	30.0 (30+0)	29+1 – 31+5	572.7 (582.0)	429.5–668.5
6	34.1 (34+1)	33+1 – 36+3	709.0 (694.8)	565.0–846.5
7	38.1 (38+1)	37+4 – 39+4	787.5 (809.3)	564.5–946.0
Delivery	40.5 (40+3)	38+6 – 42+1		

culated from both the sagittal and transversal slices. All placental volumetric analysis were done manually, following the placental borders, as the software's semi-automatic edge-detection program could not be used reliably on the placenta. One physician performed all measurements. A second physician performed random controls of the analyses for interobserver variability and deviations in the mean measured volume lay within an acceptable 10% margin.

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 21 – International Business Machines Corp., Armonk, N.Y., USA). We used the repeated measure of analysis of variance (ANOVA) for placental analysis and a linear regression analysis for analyzing placental mean growth. For the Pearson correlation between placental size and birth weight, we used placental size at 38 weeks of gestation extrapolated to the time of delivery.

All placentas were weighed during the post-partum period in their normal partly exsanguinated state.

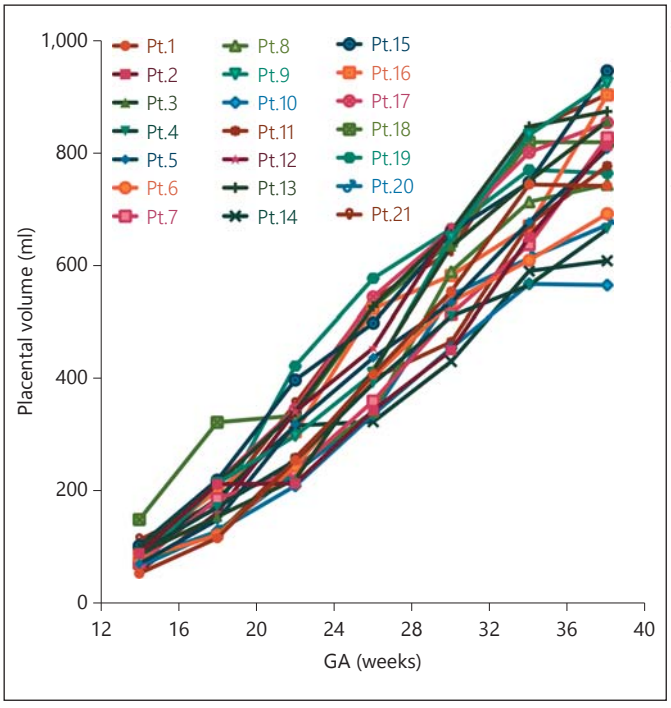

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Fig. 2. Individual placental growth.

Results

Table 1 summarizes the baseline characteristics of the volunteers. As sagittal and transversal values were similar (not shown), a mean placental volume was calculated based on the 2 measurements. The mean age of the 21 women was 31 years (range 25–37 years), mean weight was 62.7 kg (range 46–78 years) and mean weight gain during pregnancy was 15.7 kg (range 10–21 kg).

All 21 women had normal pregnancies, without any of them developing gestational diabetes, preeclampsia or other pregnancy-associated diseases. The volunteers gave birth to 12 male and 9 female infants. Seventeen children were delivered vaginally and 4 by cesarean delivery. Two cesarean deliveries were planned prior to birth – 2 were converted from vaginal delivery to operative delivery during birth due to complications, none of which involved the placenta. Deliveries occurred at mean GA of 40 weeks + 3 days (range 38 + 4 – 42 + 1). The median birth weight was 3,480 g (range 3,030–3,928 g). All children had birth weight within the 10th and 90th percentiles.

Of the 21 women, 17 (patient number 2–9, 11–17, 20 and 21) had measured placental growth curves increasing from the first to the last scan in a linear fashion. Although patient number 12 showed a steady linear growth (fig. 1) until pelvic girdle pain forced her to retire from the study; we removed the data from the analysis altogether, as data was incomplete. Four women (patient number 1, 10, 18 and 19) had placental volumes increasing until the 6th

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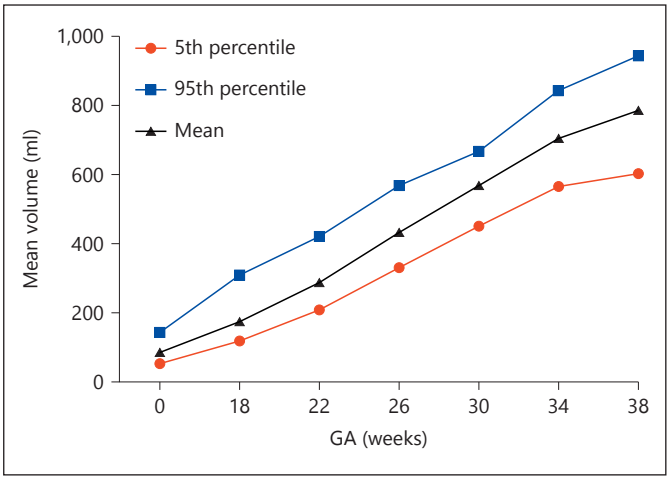

Fig. 3. Mean placental growth.

scan (GA 34) but had the same measured placental size at the 7th scan.

The placental growth curves of the 21 women are shown in figure 2. The mean placental volume of the 21 volunteers at each of the 7 sessions is illustrated in figure 3. As figure 3 presents a straight line, we used a linear regression analysis to calculate the slope, which is 29.97 ml/day ($p = 0.000$). The ANOVA analysis showed that the 7 scan means were not equal – $F(6,114) = 146$, $p = 0.003$.

The Pearson correlation between mean placental volume extrapolated to time of delivery and birth weight showed a reasonable correlation ($R = 0.56$, $p = 0.009$).

Discussion

This study is the first systematic longitudinal study of placental growth using MRI in the second and third trimesters. Although we have a small number of participants in our study, no other study have had a higher number of individual MRI scans during pregnancy, 7 each, and a total of 146.

In a majority of our volunteers, measured placental growth was continuous beyond the 38th week of gestation. In 4 cases, we did not measure an increase in placental volume after the 34th week of gestation, but in all 4 cases, fetal growth was continuous, flow in the uterine arteries was normal and thus dysfunction of the placenta was not the reason for the stagnation in size.

Thomson et al. [3] has shown that women who carried their pregnancies until term, delivered heavier placentas than women who gave birth earlier, based on a study done with 52,000 births, where placentas were weighted after delivery. This corresponds well with our results that placental growth is a continuous process during pregnancy.

Our results show a mean increase in growth until the 38th week of gestation. Two of our volunteers went into labor on days 1 and 5 after their final MRI session, providing us with accurate measured placental volume at delivery. The volume of the 2 placentas measured was 741 and 744 ml, respectively, corresponding with the slope of the mean curve in figure 3. We can therefore assume that the growth rate of the placenta, from our last MRI session at 38 GA until delivery, follows the linear slope of the mean growth rate curve. Furthermore, our latest scans in the trial were made in GA 39 + 4 in 2 cases. The volume of the placentas were 856 and 691 ml, respectively, both following their individual increasing curve of placental growth, and increasing between each scan. This indicates that the growth of the placenta continues linearly beyond 39 weeks of gestation at least.

We used the slope of the mean curve (29.97 ml mean daily increase in placental size) to calculate the estimated placental volume at the time of delivery. This estimate was used for the comparison of placental volume at the time of delivery in vivo versus the placental weight post partum. Thus, by extrapolating the curve to the time of delivery for each of the women, we found a median placental volume of 856 ml (range 602–1,050 ml).

The median weight of the delivered partly exsanguinated placenta was 640 g (range 500–787 g). The mean density of blood is 1.06 g/ml and mean placental density at term was 0.94–1.14 g/cm [3–16]. This indicates that approximately 227 ml blood escape from the placenta at the time of delivery.

Previous studies of normal placental growth have focused primarily on growth relative to placental growth in intrauterine growth restricted (IUGR) infants.

Baker et al. [9] performed an echo planar imaging (EPI) scan once in the second or third trimester in 32 singleton (36% first time) pregnancies. Eleven of the 32 infants had birthweight below the 10th percentile. The 21 infants with normal birthweight showed a placental volume curve with linear growth, with a weekly growth rate of 33.3 ml from a mean volume of 500 ml at 25 weeks of gestation (2 scans; range 375–550 ml) to a mean volume of 1,000 ml at term (4 scans; range 600–1,125 ml).

Damodaram et al. [2] performed one MRI scan on 20 IUGR fetuses and 28 normal fetuses during pregnancy; the time of the scans ranged from 23.8 to 37.7 weeks of gestation (mean 30 GA) in the normal group. These pla-

centa volumes measured at different times during pregnancy produced a curve with a linear growth rate, increasing by 0.032 mm^3 per week in the second and third trimesters (from approximately 5.50 mm^3 at 20 weeks to approximately 6.15 mm^3 at 40 weeks of gestation – which must be an error, as this corresponds to a 0.000032 ml increase per week. Perhaps 32 ml per week is more accurate).

Derwig et al. [1] performed one MRI scan during pregnancy on 83 pregnancies, 37 of which had normal intrauterine growth. In this population, the placenta was shown to grow logarithmically from 363 cm^3 at 24 GA to 515 cm^3 at 29 GA.

Andescavage et al. [17] performed a total of 112 MRI scans on 94 healthy pregnant controls with mixed parity (and on 41 pregnancies complicated by congenital heart disease) between 18 GA and 39 GA. The growth in the normal population was exponential from an estimated mean of 225 cm^3 at 18 GA to an estimated mean of 1,050 cm^3 at 39 GA.

Duncan et al. [10] performed a longitudinal study consisting of between 2 and 5 scans on 56 singleton (18 first time) pregnancies included over 2 years. Measurements were obtained using EPI sequences on a 0.5 T scanner. Placental size was analyzed among fetal, brain and liver volume. Their measured placental sizes ranged widely throughout pregnancy: from 50 to 675 ml at 19 GA to 400 to 1,700 ml at 39 GA. These rather large differences are explained in the paper as difficulty in distinction between placental edge and uterine wall. A logarithmically growing cure gave the best fit to the square root of the mean placental volume.

In this last described study by Duncan et al. [10] written in 2001, a low-field 0.5 T. scanner, with low signal-to-noise ratio (SNR) was used, which is why they had difficulties delineating the placenta. It is unclear why it took 2 years to include the 56 women with normal pregnancies. Furthermore, the MRI scans were not performed systematically and it is not reported how far apart in time the different scans were. Individual growth curves were not presented in the paper. However, in this only other longitudinal MRI study of human placental growth, they found comparable growth rates to those found in this study: 29.97 vs. 33 ml/week.

A 3D MRI sequence would have accelerated the scan time considerably and would probably also increase the accuracy of the volume measurements. This sequence was not available to us at that time. A reduction of slice thickness would reduce SNR, which could blur placental borders. We found 7 mm to be a value of good compromise between SNR and partial volume effect.

Even though we used high SNR, we did come across images where placental border detection was difficult. Based on both sagittal and transversal slices, as well as the 3D placenta model, delineation was easier and deviations between sagittal and transversal volume measurements were minimal.

Conclusion

This study is the first systematic, longitudinal MRI study of human placental growth during the second and third trimesters. We performed 7 consecutive scans with no adverse effects. MRI proved to be a feasible method to measure the intrauterine growth of the placenta in the third trimester, where ultrasound is less valuable. Normal human placenta growth was found to be linear throughout the second and third trimesters with a mean growth rate of 29.97 ml per week. The median extrapolated placental volume at delivery was to 856 ml (range 602–1,050 ml). As expected, the calculated volume was higher than the volume of the exsanguinated placenta after delivery (630 ml). Our results can be used as a normogram due to the lack of larger population studies with systematic longitudinal follow-up.

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Disclosure Statement

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