



Percentiles of intrauterine placental volume and placental volume relative to fetal volume: A prospective magnetic resonance imaging study

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ABSTRACT

Introduction: We aimed to provide percentiles of intrauterine placental growth and placental growth relative to fetal growth (placental to fetal ratio) by measuring placental and fetal volumes by magnetic resonance imaging (MRI).

Methods: In this prospective study, 107 unselected singleton pregnancies were examined by MRI at gestational week 27 and 37. Based on the estimated volumes of the placenta and the fetus, we calculated median and percentiles at gestational weeks 27 and 37.

Results: Median placental volume at gestational week 27 was 513 cm³ (Inter Quartile Range (IQR) 182 cm³), and 831 cm³ (IQR 252 cm³) at week 37. The 10th – 90th percentiles included placental volumes between 392 and 717 cm³ at gestational week 27, and 631–1087 cm³ at week 37. The placental to fetal ratio was significantly higher at gestational week 27 than at week 37, with a median ratio of 0.54 (IQR 0.18) and 0.31 (IQR 0.08), respectively ($p < 0.001$). The 10th-90th percentiles included placental to fetal ratios between 0.43 and 0.73 at gestational week 27 and 0.25–0.39 at week 37.

Discussion: At gestational week 27, the placental volume was about half the size of the fetal volume, whereas at week 37, the placental volume was about one third of the fetal volume. This finding suggests that placental growth was less prominent than fetal growth after gestational week 27. Knowledge about the distribution of intrauterine placental size in the general population of pregnancies are prerequisites for diagnosing abnormal placental size.

1. Introduction

The placental growth is vital for fetal growth. Yet, data about normal intrauterine placental growth are scarce. The present knowledge about placental growth is based mainly on placental weight at delivery [1–4]. However, pregnancies with preterm delivery may not be normal pregnancies, and underlying placental pathology may have caused the preterm delivery [5,6]. Therefore, placental size in preterm deliveries may not be representative of the placental size in pregnancies that are still ongoing. Also, the delivery in itself, placental blood loss, and preparation of the placenta prior to the weighing may affect placental weight at delivery [7].

Examination by magnetic resonance imaging (MRI) is excellent for

soft tissue volume measurements, and MRI of the pregnant uterus gives a complete overview of the fetus and the placenta [8]. MRI examinations without contrast can safely be used in the second and the third trimester of pregnancy [9]. Placental volume has been measured by MRI in previous studies [10–16]. However, in these studies most pregnancies had suspected pathology, and few pregnancies were examined by MRI more than once. Hence, our present knowledge about the intrauterine placental size and growth may be biased.

Since we have limited knowledge about intrauterine growth of the placenta in the general population of pregnancies, we cannot diagnose pregnancies with abnormal placental growth. In previous population studies of deliveries, disproportional placental weight relative to infant weight was associated with adverse outcomes for the child, such as

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stillbirth, neonatal death and cerebral palsy [17–21]. These findings were independent of the absolute birthweight of the infant. In order to identify pregnancies with disproportional placental weight relative to infant weight in pregnancies while they are still ongoing, we need to know the distribution in the general population of pregnancies of intrauterine placental growth and growth of the placenta relative to the fetus (placental to fetal ratio).

In this prospective study, we measured placental volume and placental to fetal ratio in the last part of pregnancy. We included 107 singleton pregnancies from an unselected population, and they were examined by MRI at gestational week 27 and 37. Based on the variation of volumes, we estimated percentiles of placental volume and placental

to fetal ratio.

2. Methods

We used data from the Placental Volume Study, at Akershus University Hospital in Norway. This hospital provides antenatal and obstetric health care, free of charge, for almost all pregnant women in the catchment area. During the inclusion period, from April 2017 to May 2018, a total of 5000 women were pregnant and referred to our hospital for routine fetal ultrasound examination at 17–19 weeks after their last menstrual period [22]. At this ultrasound examination, gestational age of the pregnancy was estimated by measuring fetal biparietal diameter

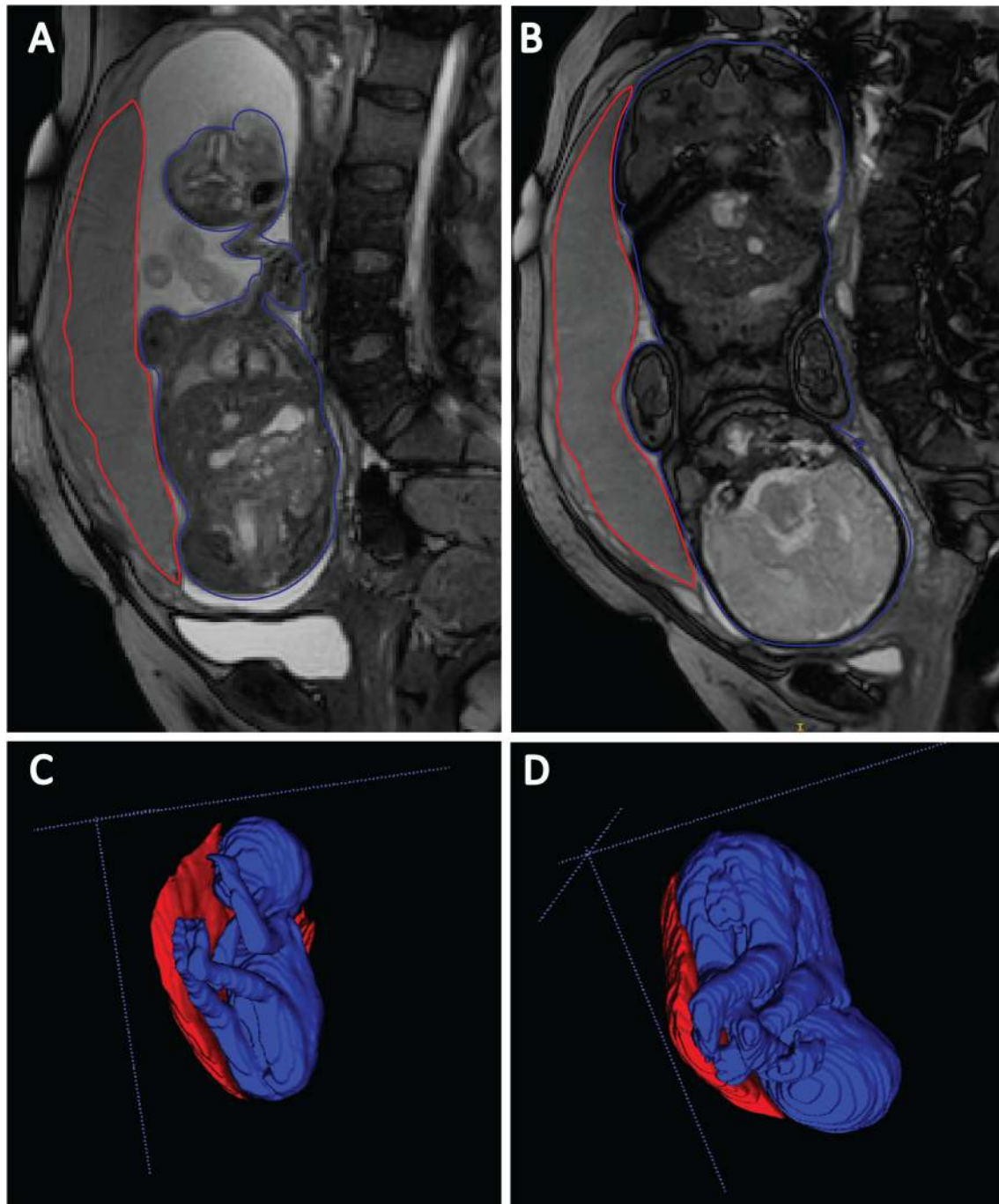


Fig. 1. Example MRI images with tracings and 3D models at gestational week 27 (A and C) and gestational week 37 (B and D). The placenta is shown in red, the fetus in blue. In this pregnancy, the placental to fetal ratio decreased from 0.76 at gestational week 27 to 0.33 at week 37.

and femur length, and represents the standard for estimation of gestational age and term date in Norway [23].

We invited to participate in the Placental Volume Study all women who were scheduled for routine fetal ultrasound examination the weekdays when we had study resources available, a total of 350 women. We did not include women with a multiple or a non-vital pregnancy, or women who did not understand any Scandinavian language or English. There were no other exclusion criteria. A total of 255 women fulfilled the inclusion criteria and gave their written consent to participate (Supplementary Fig. 1). Among these, we recruited 116 women to be examined by MRI at gestational week 27 and 37. We recruited the women who would be at gestational week 27 when we had MRI facilities available for our study (four examinations per week).

The MRI examinations were performed by using a 1.5 MRI scanner (Ingenia, Philips Healthcare, Amsterdam, Netherlands). Almost all women tolerated the MRI examination to be performed in the supine position. If not, they were examined in a slightly tilted left decubital position. An anterior abdominal coil allowed imaging of the entire uterus without repositioning of the coil. The MRI examinations of the placenta and the fetus took approximately 10 min. The MRI volumetric acquisition included one scan in three different orthogonal planes and one steady-state free-precession (balanced fast field echo: bFFE) sequence in the sagittal plane through the uterus. The bFFE sequence was acquired within 20 s of breath hold (slice thickness 5 mm (mm), no slice gap, echo time (TE) 1.7 ms (ms), repetition time (TR) 3.3 ms, field of view (FOV) 300–350 mm).

For calculations of placental and fetal volume, we used the commercially available software ITK-SNAP version 3.6.0 [24]. Firstly, we manually traced offline the borders of each slice through the placenta (approximately 50 slices), and thereafter the total placental volume was calculated by the software as the sum of the placental area in each slice (mm^2) times the slice thickness (5 mm). The fetal volume was calculated in the same manner, by offline tracing the fetal borders on each slice through the fetus (Fig. 1).

One investigator (V.H.) performed the manual tracing. Additionally, 20 of the placentas were traced by a second investigator (A.S.B) and retraced by V.H for reliability analyses. Both the interrater and the intrarater reliability of placental volume measurements were excellent, with intraclass correlation coefficients (ICC) of 0.96 (95% confidence interval 0.90–0.99, $p < 0.001$), and 0.98 (95% confidence interval 0.95–0.99, $p < 0.001$), respectively (Supplementary Fig. 2). A pediatric radiologist detected no fetal morphological anomalies by studying the MRI images.

Firstly, we calculated the median, with interquartile ranges (IQR), of placental volume, fetal volume and placental to fetal ratio at gestational week 27 and 37. The placental to fetal ratio was calculated as placental volume (cm^3)/fetal volume (cm^3).

Thereafter, we estimated percentiles of placental volume and of placental to fetal ratio at gestational week 27. Although the MRI examinations were scheduled at gestational week 27⁺⁰, the actual gestational week at the examination varied slightly. We therefore made adjustment for the actual gestational week (weeks + days) at the MRI examination by applying the Lambda Mean Standard Deviation (LMS)-polynomial regression model [25]. The distribution of placental volume, as a function of gestational week, best fitted a rectilinear curve (first order regression model), whereas the distribution of the placental to fetal ratio best fitted a parabolic curve (second order model). To correct for the skewness, the distributions of placental volume and placental to fetal ratio were Box-Cox transformed (with parameter $\lambda = -0.809$ and -1.372 , respectively). Hence, the regression residuals became normally distributed with uniform dispersion (σ) over the actual range of gestational weeks, and percentiles (2.5, 5, 10, 25, 50, 75, 90, 95 and 97.5 percentiles) for the residuals could be calculated. Percentiles in the original units (cm^3) were obtained by inversion of the regression equations, followed by subsequent retransformation (invers Box-Cox).

We repeated the above calculations by using the MRI results at

gestational week 37. At this gestational week, the distribution of both placental volume and placental to fetal ratio, as a function of the actual gestational week, best fitted a rectilinear curve, and the distributions were Box-Cox transformed with the parameters; $\lambda = 0.911$ and $\lambda = 0.060$, respectively.

Finally, we interpolated values for placental volume and placental to fetal ratio for the interval between gestational weeks 27 and 37 for which we had no data. Previous studies with frequent MRI measurements of the same placenta during the gestational weeks 27–37 suggest linear growth within this interval [15,16].

The statistical analyses were performed by using SPSS Statistics, version 25 and Excel, Microsoft 2010.

The Regional Committee for Medical and Health Research Ethics, South East Norway, approved the study (reference number: 2016/1185 A).

3. Results

Out of the 116 women scheduled for MRI examinations, nine women cancelled their appointments at gestational week 27, leaving 107 women to be examined. For three of these women their MRI images could not be used due to artifacts. At gestational week 37, at total of 89 women were examined. Five women had delivered before their scheduled appointment, and 13 women cancelled their appointments for various reasons. Thus, images from a total of 193 MRI examinations could be included in our data analyses.

The women's median age was 31.6 years, and 45% ($n = 48$) had no prior delivery. At the first MRI examination, median gestational week was 27⁺⁰. At the second MRI examination, median gestational week was 36⁺⁵ (Table 1).

The median placental volume was 513 cm^3 (IQR 182 cm^3) at gestational week 27 and, it was 831 cm^3 (IQR 252 cm^3) at gestational week 37 (Table 2, Fig. 2A). There was a large difference between the largest and the smallest placenta, both at gestational week 27 and at gestational week 37 (Figs. 2A and 3A).

The median fetal volume was 951 cm^3 (IQR 149 cm^3) at gestational week 27 and 2721 cm^3 (IQR 384 cm^3) at gestational week 37.

At gestational week 27, the median placental to fetal ratio was 0.54 (IQR 0.18) (Table 2, Fig. 2B), and at gestational week 37, the median placental to fetal ratio was 0.31 (IQR 0.08) (Table 2, Fig. 2B). Thus, fetal growth was more pronounced than placental growth after gestational week 27.

At gestational week 27, the 10th – 90th percentiles included placental volumes between 392 cm^3 and 717 cm^3 (Fig. 3A). At gestational week 37, the 10th-90th percentiles included placental volumes

Table 1
Characteristics of the study sample ($n = 107$) with median and Interquartile range (IQR).

	N (proportion, %)	Median (IQR)
No prior delivery	48 (45)	
Pregnancy after in vitro fertilization	5 (4.7)	
Maternal diabetes ^a	5 (4.7)	
Maternal hypertensive disorder ^b	10 (9.0)	
Maternal age, years		31.3 (5.7)
Gestational week at the first MRI examination (weeks + days), $n = 104$		27 + 0 (6)
Gestational week at the second MRI examination (weeks + days), $n = 89$		36 + 5 (6)
Cesarean delivery	22 (20.7)	
Assisted vaginal delivery (vacuum or forceps)	9 (8)	
Male sex of the fetus	47 (44)	
Birth weight (grams), $n = 106$		3605 (641)
Placental weight (grams), $n = 102$		620 (211)

^a Includes pre-gestational diabetes and gestational diabetes.

^b Includes preeclampsia, gestational hypertension and chronic hypertension.

Table 2

Median and mean placental volume, fetal volume and placental to fetal ratio as measured by MRI examinations at gestational weeks 27 and 37. Placental to fetal ratio is calculated as placental volume cm³/fetal volume cm³.

	Placental volume (cm ³)		Fetal volume (cm ³)		Placental to fetal ratio	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
Gestational week 27 (n = 104)	513 (182)	536 (137)	951 (149)	963 (111)	0.54 (0.18)	0.56 (0.12)
Gestational week 37 (n = 89)	831 (252)	845 (183)	2721 (384)	2703 (310)	0.31 (0.08)	0.31 (0.05)

SD= Standard Deviation, IQR= Interquartile Range.

between 631 cm³ and 1087 cm³.

The 10th – 90th percentiles of placental to fetal ratio included values between 0.43 and 0.73 at gestational week 27, and between 0.25 and 0.39 at gestational week 37 (Fig. 3B). Fig. 3A and B also show the interpolated percentiles of placental volume and placental to fetal ratio between the gestational weeks 27 and 37.

4. Discussion

We found a large variation of intrauterine placental volume. At gestational week 27, the 10th – 90th percentiles included placental volumes between 392 cm³ and 717 cm³. At gestational week 37, the 10th-90th percentiles included placental volumes between 631 cm³ and 1087 cm³. Fetal growth was more prominent than placental growth, and median placental to fetal ratio decreased from 0.54 to 0.31 during the gestational weeks 27–37.

Previous MRI studies of placental volume are few. In five MRI studies, the placental volume was measured once only, and the measurement was performed at various time points between gestational week 6 and 39 [10–14]. These studies included pregnancies with and without fetal pathology. Among the pregnancies without fetal pathology, however, the reported mean placental volume was comparable to our findings at the corresponding gestational week.

To our knowledge, only two prior studies comprise more than one

MRI examination of the same placenta [15,16]. In the first study, 56 pregnancies were examined a maximum of five times after gestational week 19 [15]. This study reports slightly larger median placental volumes than our study: 642 ml at gestational week 27 and 1107 ml at gestational week 37. The corresponding placental to fetal ratio was 0.66 and 0.40. The range of placental volumes was wide at gestational week 37 (650 ml-1800 ml). In the second study, 21 healthy first time mothers with normal body mass index were included at gestational week 14, and seven MRI examinations were performed of each placenta [16]. They reported median placental volume at gestational week 26 was 409 ml, and it was 809 ml at gestational week 38. The increase in placental volume between gestational week 27 and 37 was similar to our findings, approximately 300 ml, and placental growth was reported to be linear. As far as we know, our study is the largest yet to report intrauterine placental volume measured at more than one time point in pregnancy. We are not aware of any previous prospective MRI studies of placental to fetal ratio.

MRI is increasingly used during pregnancy [26]. Our study provides percentiles of placental volume and placental volume relative to fetal volume in ongoing pregnancies. Such values are prerequisites for diagnosing abnormal placental size for gestation. Our results may also be used to study associations of intrauterine placental size with fetal weight, blood flow in the fetal-placental arteries, and pregnancy outcomes. Few studies yet have addressed the relation of placental volume with clinical measures used to identify high risk pregnancies [12,13]. Such studies require a larger study sample than ours to provide precise estimates of associations. It is conceivable that information about the percentile of placental volume for an individual pregnancy may provide additional information about the risk of adverse outcome. Several previous studies of deliveries have suggested that abnormal placental size, and disproportionality between placental and fetal size may be a sign of fetal failure to thrive [17–21,27–30].

In our study, median intrauterine placental volume in gestational week 37 was 813 cm³, and median placental weight at the delivery was 623 g. This discrepancy suggests that placental volume in cubic centimeters may not equal weight in grams, or that the shape and the weight of the placenta change during labor or shortly after the delivery [31]. Delivered placentas can therefore not be used for estimation of percentiles of the intrauterine placental size.

MRI is considered an expensive and inconvenient tool in the

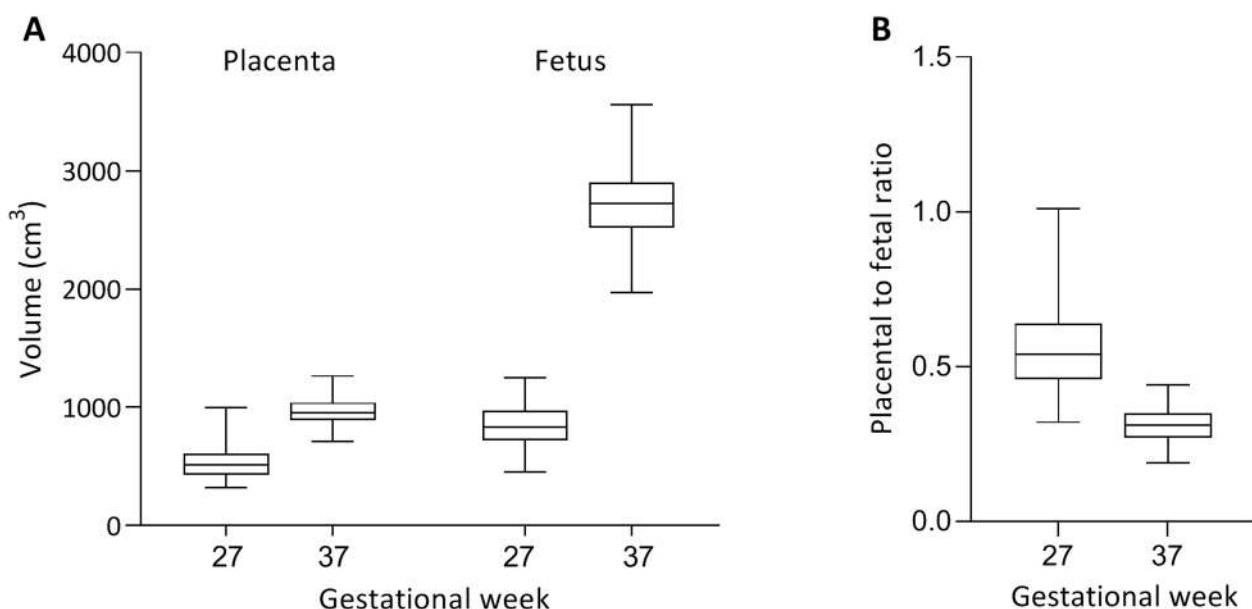


Fig. 2. Median placental and fetal volume (cm³) (A), and median placental to fetal volume ratio (B) at gestational week 27 and 37. Also interquartile ranges and minimum and maximum values are presented. Placental to fetal ratio is calculated as placental volume cm³/fetal volume cm³.

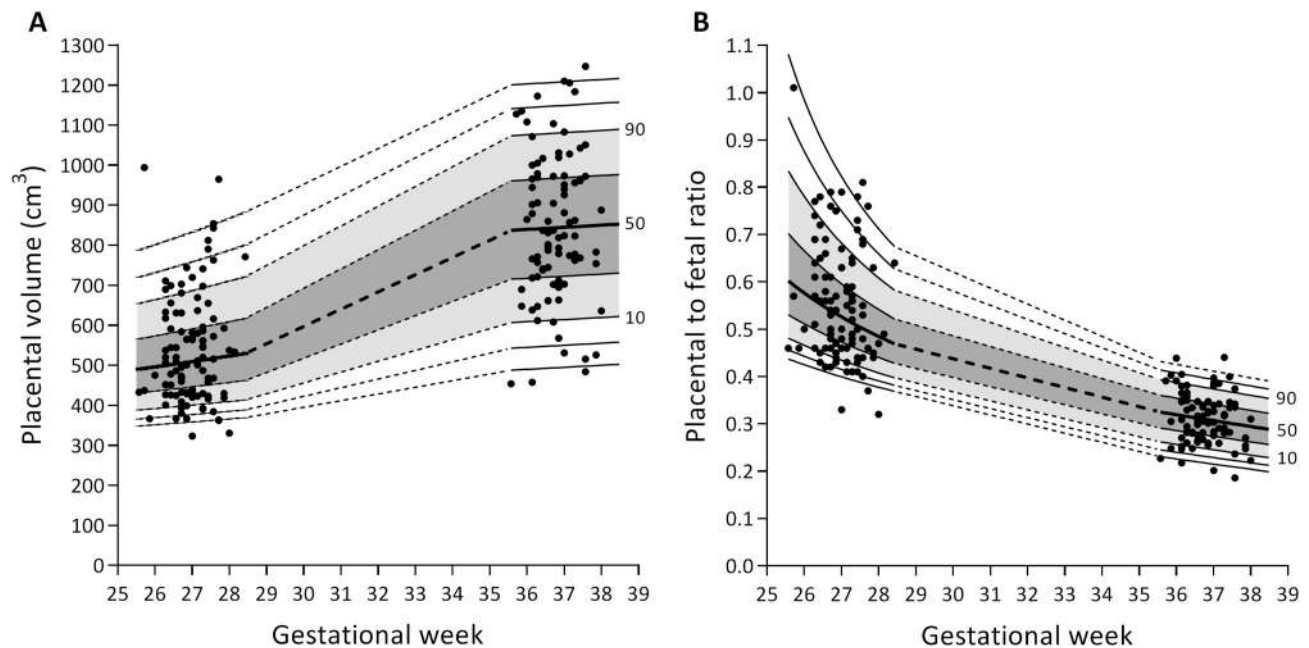


Fig. 3. Percentiles (2.5, 5, 10, 25, 50, 75, 90, 95, and 97.5) of placental volume (A) and placental to fetal ratio (B) by gestational week. The estimates are based on 107 pregnancies examined by MRI in pregnancy week 27 and/or 37. The black dots represent measurements of each pregnancy at the exact gestational age.

diagnostics of pregnancies, and ultrasound is presently the diagnostic tool of choice. However, ultrasound examinations do not yet provide valid placental volume measurement in the last part of pregnancy [32]. However, percentiles of placental volume may also be important for the development and use of ultrasound for placental measurements.

The pregnancies in our study sample were similar to pregnancies in Norway in general. At the delivery, mean birthweight and mean placental weight in our study, were in line with all births in Norway during our study period [33]. Thus, we believe that the placental percentiles estimated in our study may be applicable to populations of pregnancies that are similar to the pregnancies in Norway. It is well known that birthweight, and probably also placental weight, vary across populations. Thus, our results may not be generalizable to populations with different birthweight distributions.

The number of individuals needed to calculate percentiles at the edges of the distributions is estimated to be 120 [34]. We aimed to include a number of participants as close as possible to this recommendation. However, for practical reasons the final number reached 104 only. A reduction from 120 to 104 individuals will still provide an acceptable precision, according to standard formulas for estimation of sample size [35]. However, the percentiles at the edges of the distributions may be uncertain.

MRI is a tool for valid organ volume measurements, and the uterus as a whole can be imaged throughout pregnancy [8]. Delineation between the placenta and the uterine wall was difficult in a few images and may account for measurement errors. However, the intrarater and interrater reliability of the MRI placental volume measurements were excellent. Fetal movements made fetal volume measurement difficult in a small number of examinations (less than 5), and previous studies have shown MRI to be accurate in estimation of fetal weight [36,37].

Our study included MRI examinations at the gestational weeks 27 and 37, and we assumed linear placental and fetal growth between these time points. Although suggested by previous studies of placental growth, such assumption may not be true and should be tested in larger study samples than ours and with more frequent MRI examinations [15,16].

In this study, we present percentiles of placental volume and placental to fetal ratio among unselected pregnancies at gestational weeks 27–37. Our results may be useful in the diagnostics of abnormal intrauterine placental growth.

Contribution to authorship

A.E., V.H, K.G., A.B. and H.F.P. had the original idea for this study. Data collection was performed by V.H. and S.S. V.H., L.M., S.S. and H.F.P. performed the data analyses. A.E., V.H. H.F.P. and L.M. interpreted the results and wrote the manuscript. All authors have and critically revised the manuscript. A.E. is the guarantor of the study. All authors have full access to the data and can take responsibility for the integrity of the data and the accuracy of the data analyses, they have approved the submitted version of the manuscript and report no conflicts of interests.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.placenta.2022.02.023>.

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