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ORIGINAL RESEARCH

# Placental size and umbilical vein volume blood flow

Kari Flo[1] | Carl Petter Skaar Kulseng[1,2] | Helene Fjeldvik Peterson[1,3] | Vigdis Hillestad[3,4] | Silje Sommerfelt[1] | Anne Eskild[1,3]

[1]Division of Obstetrics and Gynecology, Akershus University Hospital, Lørenskog, Norway

[2]Sunnmøre MR-Klinikk, Ålesund, Norway

[3]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[4]Department of Diagnostic Imaging, Akershus University Hospital, Lørenskog, Norway

**Correspondence**
Anne Eskild, University of Oslo, Institute of Clinical Medicine, Campus Akershus University Hospital, N-1478, Lørenskog, Norway.
Email: anne.eskild@medisin.uio.no

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## Abstract

**Introduction:** The fetus receives oxygen and nutrition from the placenta through the umbilical vein. There is a large variation in placental size and placental size relative to fetal size (placental–fetal ratio). We studied whether placental size or placental–fetal ratio is related to blood flow in the umbilical vein.

**Material and Methods:** We performed a prospective study at Akershus University Hospital in Norway and a total of 73 women were examined in gestational weeks 27 and 37. Fifty-six women were examined at both time points. B-mode ultrasound and Doppler ultrasonography were used to measure the umbilical vein volume blood flow per minute. Magnetic resonance imaging was used to measure placental and fetal volume. Pearson's and Spearman's correlation coefficients were applied for estimations of associations.

**Results:** In gestational week 27, the umbilical vein volume blood flow was positively correlated with fetal size (Pearson's correlation coefficient $r=0.372$, $p=0.003$, and Spearman's correlation coefficient $r=0.384$, $p=0.002$), but not with placental size (Pearson's $r=0.130$, $p=0.317$, and Spearman's $r=-0.53$, $p=0.687$) or placental–fetal ratio (Pearson's $r=-0.61$, $p=0.641$, and Spearman's $r=-0.218$, $p=0.092$). In gestational week 37, we found positive correlations of the umbilical vein volume blood flow with fetal size (Pearson's $r=0.428$, $p=<0.001$, and Spearman's $r=0.391$, $p<0.001$), placental size (Pearson's $r=0.400$, $p=0.001$, and Spearman's $r=0.643$, $p<0.001$), and with placental–fetal ratio (Pearson's $r=0.224$, $p=0.066$, and Spearman's $r=0.266$, $p=0.028$).

**Conclusions:** A large placenta and a high placental–fetal ratio are associated with increased umbilical vein blood flow.

KEYWORDS
Doppler, magnetic resonance imaging, placenta, pregnancy, ultrasound, umbilical vein

**Abbreviation:** MRI, magnetic resonance imaging

## 1 | INTRODUCTION

Normal placental development and growth are crucial for fetal well-being. The placenta supplies oxygen and nutrients to the fetus through the umbilical vein, and the volume blood flow in the umbilical vein is positively associated with fetal growth and birthweight.[1–7] It is not known whether blood flow in the umbilical vein is associated with placental growth or placental size. Placental size has, until recently, been unavailable for measurements since it cannot easily be measured by ultrasound in ongoing pregnancies.[8] However, magnetic resonance imaging (MRI) may now provide reliable measures of in-utero placental volume.[8–11]

There are no studies of the relation between placental size relative to fetal size (placental–fetal ratio) and the volume of blood flow of the umbilical vein. Such knowledge may increase our understanding of placental–fetal circulation and the impact of placental and fetal size.

We hypothesize that placental size and placental–fetal ratio are positively associated with umbilical vein volume blood flow. Thus, we aimed to study the association of umbilical vein volume blood flow with placental size and placental–fetal ratio in ongoing pregnancies. Placental and fetal size were measured by MRI.

**Key Message**

Placental size and placental size relative to fetal size correlated with umbilical vein volume blood flow in gestational week 37. Fetuses with a large placental–fetal ratio receive more blood than fetuses with a smaller placenta independent of estimated fetal weight.

## 2 | MATERIAL AND METHODS

We used data from a prospective study of placental growth, the Placental Volume (PLAVO) Study. The women were examined in gestational week 27 and 37. The study participants were selected among all pregnant women who underwent routine fetal ultrasound examination at Akershus University Hospital in Norway during the period April 2017 through May 2018. Since the research resources for MRI examination were limited, we chose for inclusion the women who were in gestational week 27 on the weekdays with available resources (approximately once a week). There were no exclusion criteria except a non-viable pregnancy, multiple pregnancy, or not being able to understand English or a Scandinavian language. Our study sample was restricted to women with MRI examination and measurements of the umbilical vein volume blood flow at one or both time points in pregnancy, a total of 73 women of whom 61 women were in gestational week 27 and 68 women were in gestational week 37. A total of 56 women had measurements at both time points. Sample characteristics and pregnancy outcome were retrieved from hospital records.

We estimated placental and fetal size in utero by MRI.[8,9] Size was estimated as volume in cubic centimeters ($cm^3$). A 1.5 T MRI scanner (Ingenia; Philips Healthcare) was used for all examinations. An anterior abdominal coil allowed examination of the entire uterus without repositioning. The volumetric acquisitions of the placenta and fetus included a steady-state free-precession (balanced fast field echo:bFFE) sequence through the uterus (slice thickness 5 millimeters (mm), no slice gap, echo time (TE) 1.7 milliseconds (ms), repetition time (TR) 3.3 ms, field view (FOV) 300–350 mm). In-plane resolution was 1 mm × 1 mm. This sequence was acquired within 20 s of maternal breath holding, and one scan was made of each placenta and fetus unless technical problems occurred. Most women were examined in the supine position. Women who did not tolerate the supine position were examined in a slightly tilted left decubital position. The placental and fetal borders on each MRI image (5 mm slices) through the uterus were traced manually by one single examiner (VH). The placental and fetal volumes were calculated based on the area of interest in each slice ($mm^2$) and the distance between the slices (5 mm) by using the commercially available software ITK-SNAP (ITK-SNAP version 3.6.0). The decidual layer of the placenta was not included as a part of the placenta. One investigator (VH) performed all the tracings. The placental–fetal ratio was calculated as: placental volume ($cm^3$)/fetal volume ($cm^3$).

We measured the umbilical vein volume blood flow by ultrasound (Volusone E8, GE Healthcare). The measurements were performed on the same day as the MRI examination for almost all women, and the interval between the MRI examination and umbilical vein blood flow measurements was no longer than two days for any woman. All umbilical vein blood flow measurements were performed at the free loop of the umbilical cord while the fetus was not moving. The umbilical vein measurements were performed by one examiner (S.S), and she measured the volume of blood (milliliter / minute (ml/min)) passing through the umbilical vein to the fetus. The measurements were performed as follows: Firstly, she measured the diameter of the umbilical vein with two-dimensional (2D) ultrasound using an enlarged, frozen B-mode image, and the angle of insonation was kept as close to 90 degrees as possible. The caliper was placed on the lines representing the inner walls of the umbilical vein. The cross-sectional area ($cm^2$) of the umbilical vein was calculated as: 3.14 × (diameter/2).[2] Thereafter, she measured the time-averaged maximum velocity (TAMXV) centimeters/second (cm/s) of the blood flow in the umbilical vein by using color Doppler ultrasound. The angle of insonation was kept as small as possible and not above 15 degrees. The mean velocity (cm/s) was calculated as: 0.5 × TAMXV. Finally, the umbilical vein volume blood flow (ml/min) was calculated as: cross-sectional area ($cm^2$) × mean velocity (cm/s) × 60.[12,13]

### 2.1 | Statistical analyses

We present the distributions of study factors as means with standard deviations (SD) and as medians with ranges. The strength of the

correlation of placental size with umbilical vein volume blood flow was estimated by applying Pearson's and Spearman's correlation analyses. We also estimated the correlation of fetal size and placental–fetal ratio with the umbilical vein volume blood flow. The above correlations were estimated in gestational week 27 and in gestational week 37. The statistical analyses were performed by using the IBM SPSS statistics for windows, version 26 (IBM Corp).

## 3 | RESULTS

Mean maternal age was 31 years (SD 4.38), pre-pregnancy body mass index was 25 kg/m$^2$ (SD 4.61), and 45% were nulliparous. No serious maternal or fetal complications were diagnosed during pregnancy (Table 1). Mean placental size was 534.52 cm$^3$ (SD 141.20) in gestational week 27 and 841.46 cm$^3$ (SD 191.99) in gestational week 37 (Table 2). The placental–fetal ratio was 0.55 (SD 0.12) in gestational week 27 and 0.31 (SD 0.06) in gestational week 37 (Table 2). Mean umbilical vein blood flow was 146.27 mL/min (SD 41.23) in gestational week 27 and 320.74 mL/min (SD 128.76) in gestational week 37 (Table 2).

In gestational week 27, we found no correlation of placental size with umbilical vein volume blood flow (Pearson's correlation coefficient $r=0.130$, $p=0.317$ and Spearman's correlation coefficient $r=-0.53$, $p=0.687$). There was a positive correlation of fetal size with umbilical vein volume blood flow (Pearson's correlation coefficient $r=0.372$, $p=0.003$ and Spearman's correlation coefficient $r=0.384$, $p=0.002$), but no correlation of placental–fetal ratio with umbilical vein volume blood flow (Pearson's correlation coefficient $r=-0.061$, $p=0.641$ and Spearman's correlation coefficient $r=-0.218$, $p=0.092$) (Figure 1 and Table 3).

In gestational week 37, we found a positive correlation of placental size with umbilical vein volume blood flow (Pearson's correlation coefficient $r=0.400$, $p<0.001$ and Spearman's correlation coefficient $r=0.643$, $p<0.001$). Also, the correlations of fetal size and placental–fetal ratio with umbilical vein volume blood flow were positive (Pearson's correlation coefficient $r=0.428$, $p<0.001$, and $r=0.224$, $p=0.066$ and Spearman's correlation coefficient $r=0.391$, $p<0.001$, and $r=0.266$, $p=0.028$ respectively) (Figure 2 and Table 3).

In supplemental analyses, we removed four outlying umbilical vein volume blood flow measures (one measure in gestational week 27 and three in gestational week 37, Figures 1 and 2), and the point estimated correlations became stronger (Table S1).

## 4 | DISCUSSION

In this study, we found positive correlations of placental size and placental–fetal ratio with umbilical vein volume blood flow in gestational week 37, but no correlations in gestational week 27. The correlation of fetal size with umbilical vein volume blood flow was positive at both time points.

**TABLE 1** Maternal and fetal characteristics of the study sample, $N=73$. Measurements are given as means with standard deviations (SD), median with range, or *N* (%) as appropriate.

| | Mean (± SD) | Median (Range) | *N* (%) |
|---|---|---|---|
| Age (years) | 31 (4.50) | 30 (21–44) | |
| Para 0 | | | 33 (45) |
| Para ≥1 | | | 40 (55) |
| Prepregnancy BMI (kg/m$^2$) | 25 (4.63) | 24 (18–39) | |
| Mean arterial pressure (mmHg) 27 weeks | 83.21 (7.70) | 82.67 (67–102) | |
| Mean arterial pressure (mmHg) 37 weeks | 88.11 (8.10) | 87.50 (66–110) | |
| Gestational age at delivery (days) | 281 (8.85) | 282 (254–297) | |
| Birthweight (g) | 3562.25 (574.62) | 3605.00 (2335–5210) | |
| Placental weight (g) | 646.04 (148.11) | 645.00 (370–990) | |
| Apgar score at 5 min | 10 (0.7) | 10 (6–10) | |

**TABLE 2** Placental size, fetal size, placental–fetal ratio, and umbilical vein volume blood flow of the study sample.

| | Gestational week 27 | Gestational week 37 |
|---|---|---|
| | Mean (SD) | Mean (SD) |
| Placental size (cm$^3$) | 534.52 (±141.20) | 841.46 (±191.99) |
| Fetal size (cm$^3$) | 963.98 (±109.97) | 2678.84 (±330.78) |
| Placental–fetal ratio | 0.55 (±0.12) | 0.31 (±0.06) |
| Umbilical vein volume blood flow (mL/min) | 146.27 (±41.23) | 320.74 (±128.76) |

*Note*: Measurements are given as means with standard deviations (SD).

We are not aware of any previous studies of the relation of umbilical vein volume blood flow with placental size or with placental–fetal ratio. It is known, however, that the umbilical vein volume blood flow is positively correlated with estimated fetal weight, fetal growth, and birthweight,[1–7] and these previous findings agree with our results.

Placental size in our study aligns with other studies that used MRI to estimate placental size. In a cross-sectional study, Leon et al. found a mean placental volume of 460.8 mL (range 259–637 mL) in gestational weeks 25–27 and 1039.3 mL (range 883–1262) in gestational weeks 37–40.[10] Derwig et al. report an increase in placental

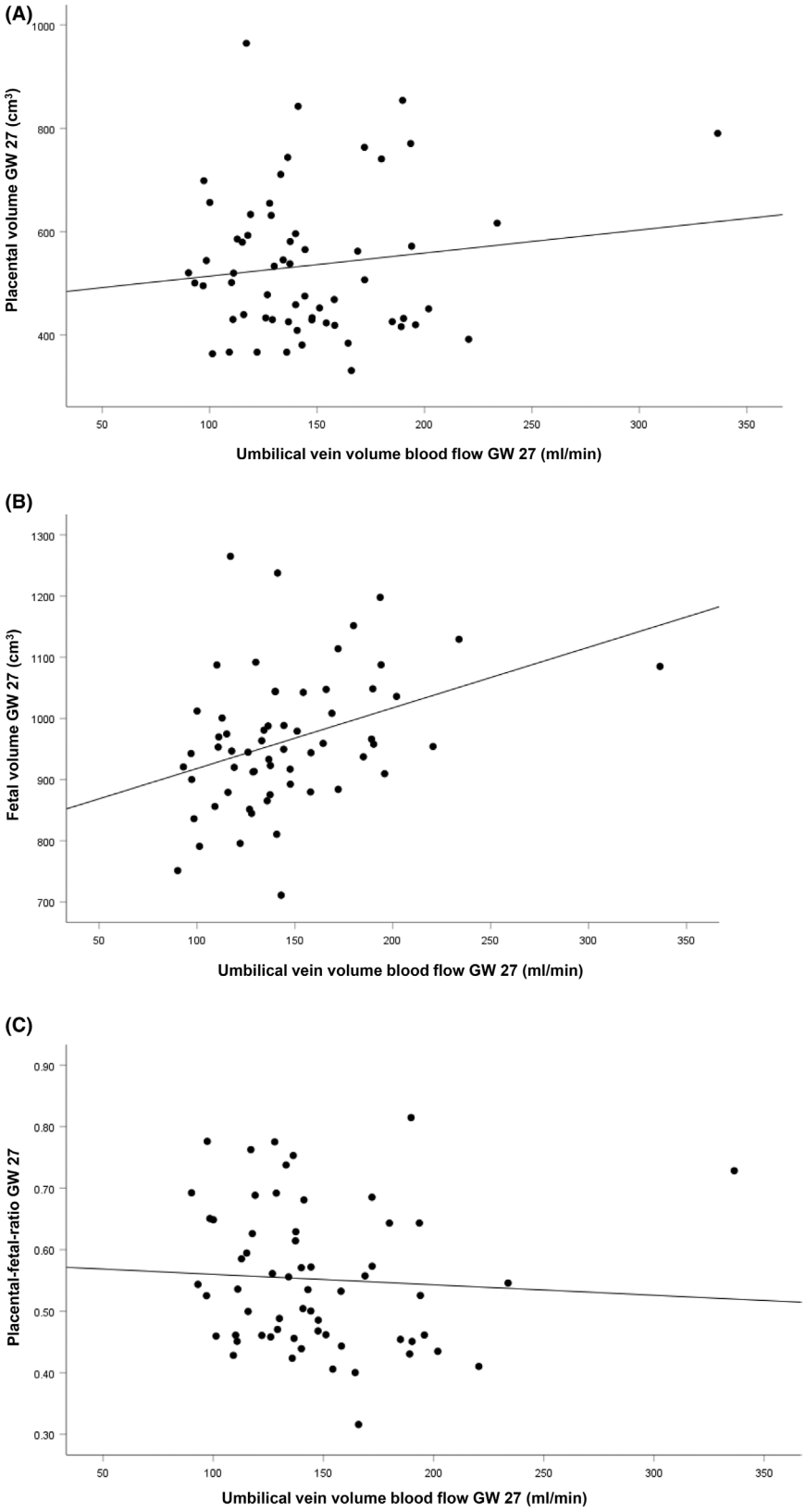



**FIGURE 1** The correlation of (a) placental size (r = 0.130, $p = 0.317$), (b) fetal size (r = 0.372, $p = 0.003$), and (c) placental–fetal ratio (r = − 0.061, $p = 0.641$) with umbilical vein volume blood flow at gestational week (GW) 27. Estimated by Pearson's correlation coefficient.

volume from 363 to 515 $cm^3$ from gestational week 24 to 29 in the normal pregnancies.[11]

The umbilical vein volume blood flow in our study is in line with some previous studies. Barbera et al. report an increase from 54 mL/min in gestational week 23 to 320 mL/min in gestational week 38.[1] Wang et al. found an increase from 32.6 mL/min in gestational week 20 to 381.9 mL/min in gestational week 39.[14] Mean blood flow in the umbilical vein is also reported to be lower than in our study.[13,15] A review from 2023 of 14 studies reports values of mean blood flow in the umbilical vein in agreement with the

**TABLE 3** The correlation of placental size with umbilical vein volume blood flow. The correlations of fetal size and placental–fetal ratio with umbilical vein volume blood flow are also presented.

| | Gestational week 27 | Gestational week 37 |
|---|---|---|
| **Correlation coefficient** | **Umbilical vein volume blood flow** | |
| Pearson | | |
| Placental size | 0.130 (0.317) | 0.400 (0.001) |
| Fetal size | 0.372 (0.003) | 0.428 (<0.001) |
| Placental–fetal ratio | −0.61 (0.641) | 0.224 (0.066) |
| Spearman | | |
| Placental size | −0.53 (0.687) | 0.643 (<0.001) |
| Fetal size | 0.384 (0.002) | 0.391 (<0.001) |
| Placental–fetal ratio | −0.218 (0.092) | 0.266 (0.028) |

distribution in our study.[16] Thus, we believe that our study sample is not skewed and that our findings may be generalizable.

The umbilical vein transports blood from the placenta to the fetus. The positive correlation of fetal size with volume blood flow in the umbilical vein may therefore be explained by a higher need for oxygen and nutrients of a large fetus compared to a small fetus.

During a normal pregnancy, the placental–fetal ratio decreases, and in gestational week 27, placental size is much larger relative to fetal size than in gestational week 37.[9] The lack of significant correlation of placental size with umbilical vein volume blood flow in gestational week 27 may therefore be explained by the large placenta, which may have excess capacity to provide the relatively smaller fetus with blood. Previous studies support such an assumption, since the volume blood flow in the umbilical vein, adjusted for estimated fetal weight, decreases during pregnancy.[1,7,13,15] Thus, the blood supply from the placenta to the fetus in gestational week 27 may be abundant and with sufficient reserve capacity independent of placental size. In gestational week 37, placental size is much smaller relative to fetal size, and the fetal demand for blood is higher. The availability of blood and oxygen may therefore be less abundant, and our findings suggest that a large placenta provides more blood to the fetus per minute than a small placenta. Population studies suggest adverse outcomes for babies with a small placenta.[17–19] The results of our study could suggest reduced blood flow from the placenta to the fetus in these pregnancies.

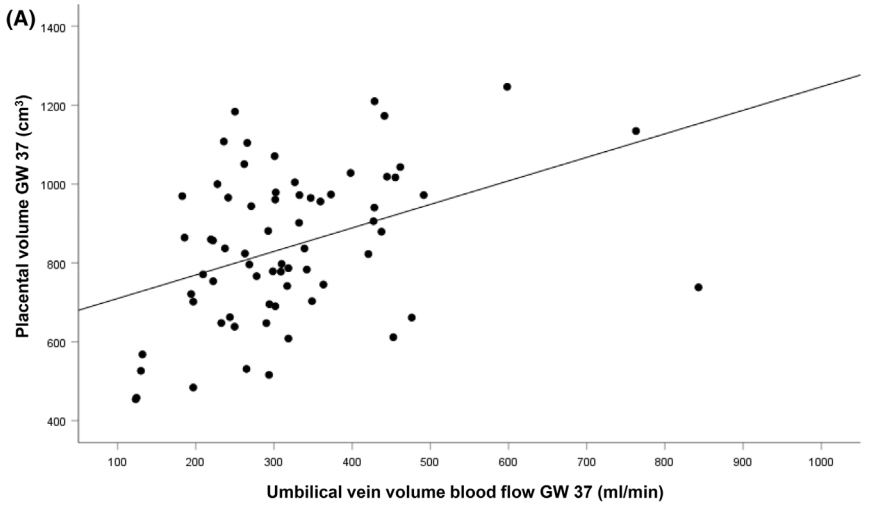
There is a large variation in placental weight and in placental–fetal ratio between pregnancies at the same gestational age. The mechanisms resulting in a small or large placenta (or a small or a large placental–fetal ratio) are not quite clear. The remodeling of the uteroplacental vessels is crucial for placental growth and development,[20] and it is plausible that insufficient remodeling of these vessels can result in a small placenta with reduced capacity to provide the growing fetus with oxygen and nutrients. One study found that chronic hypertension was associated with both low placental weight and low placental–fetal ratio.[17] Placental abnormalities such as velamentous cord insertion and a short umbilical cord were associated with a small placenta when adjusted for gestational age.[17] Preeclampsia and smoking were also associated with low placental weight, but this association disappeared when adjusting for birthweight.[17]

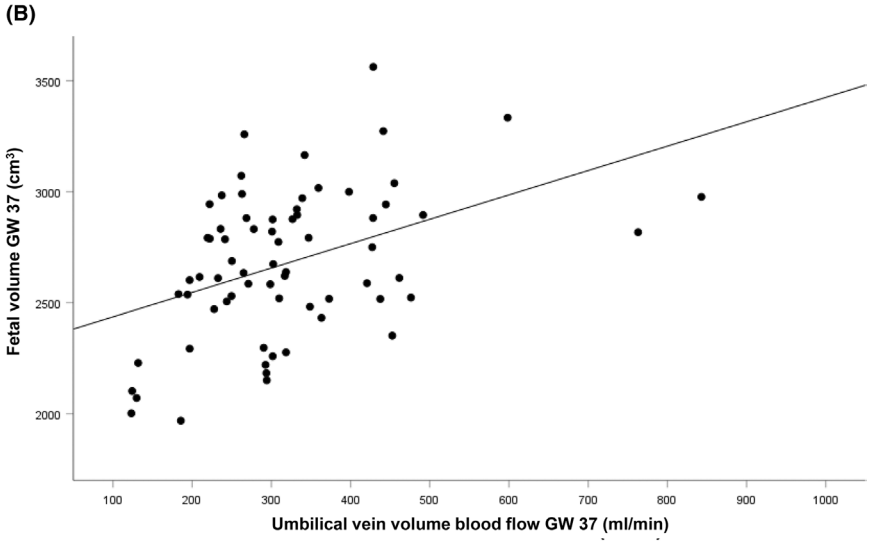
Previous studies suggest that pregnancies with maternal risk factors such as smoking, low hemoglobin levels, and preeclampsia have increased placental–fetal ratio.[21–23] These results suggest that increased placental–fetal ratio could be a response to reduced oxygen supply to the fetus. The findings in this study support such assumptions, since pregnancies with high placental–fetal ratio have increased volume blood flow through the umbilical vein. Our findings suggest that a large placenta and a large placental–fetal ratio in gestational week 37 are positively related to the blood flow to the fetus.

Disproportionate placental size relative to fetal size is related to increased risk of adverse pregnancy outcomes, and both low and high placental weight relative to infant weight at birth have been associated with increased risk.[17–19,21–25] Low placental weight or low placental–fetal ratio is associated with stillbirths[18] and cerebral palsy.[19] High placental weight or high placental–fetal ratio have been associated with neonatal morbidities such as low Apgar scores, respiratory morbidity, neonatal seizures, and NICU admission.[24,25] Among preterm deliveries also high placental–fetal ratio has been shown to be associated with fetal death,[18] neonatal death[26] and cerebral palsy.[19] These studies are all based on placental weight measured after delivery. Identification of a large or a small placenta relative to fetal size during pregnancy, however, is not easy since placental size is not yet reliably measured by ultrasound.[8] Identification of pregnancies with disproportionate placental size is of particular interest if the fetus has normal size since these pregnancies are not easily identified as high-risk pregnancies. Umbilical vein volume blood flow could possibly be used as an indicator of disproportional placental size relative to fetal size.

Our study is relatively small and includes mostly uncomplicated pregnancies with appropriate for gestational age fetuses. Despite the small number of pregnancies and the limited variations in measurements, we found significant associations in gestational week 37 suggesting true relations. In gestational week 27, a relation of placental size and placental–fetal ratio with umbilical vein volume blood flow was not estimated, possibly due to the small number of pregnancies (type two error). At both gestational weeks, the estimated associations were strengthened after omitting outlying values. This observation suggests that our results are valid. Possibly, in a larger sample with more variation in placental and fetal size and also in pregnancy outcomes, stronger associations may possibly be reached, also in gestational week 27.

We accounted for possible nonlinear associations of umbilical vein volume blood flow with placental and fetal size and placental–fetal ratio by applying the Spearman's correlation test. We did not have statistical power to further investigate patterns of possible non-linear associations. Some factors such as maternal body mass index[27] and hemoglobin levels[22] may affect placental size and



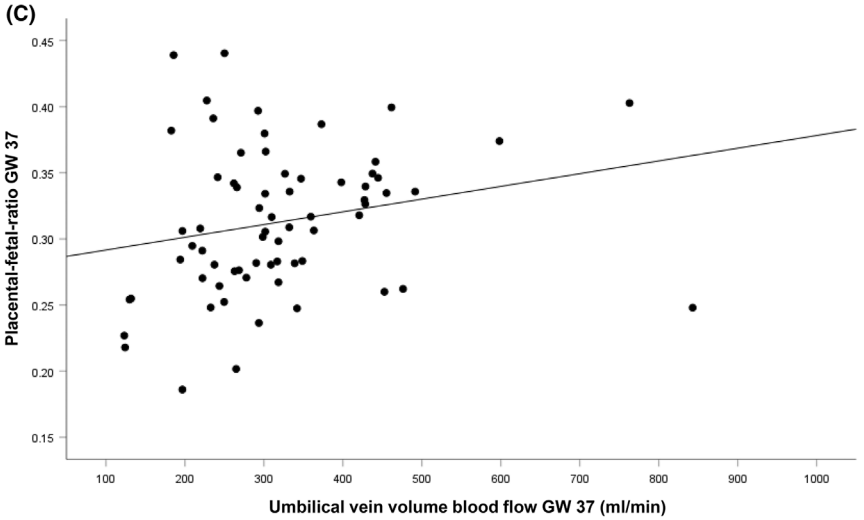




**FIGURE 2** The correlation of (a) placental size ($r=0.400$, $p<0.001$), (b) fetal size ($r=0.428$, $p<0.001$), and (c) placental–fetal ratio ($r=0.224$, $p=0.066$) with umbilical vein volume blood flow at gestational week (GW) 37. Estimated by Pearson's correlation coefficient.

placental–fetal ratio, but we are not aware of any factors that may confound the association of placental size or placental–fetal ratio with umbilical vein volume blood flow. Hence, no known factors can be adjusted for in our analyses. In clinical practice, crude measures are used and adjusted associations may not be relevant.

Measurements of the umbilical vein volume blood flow can be challenging when the fetus is moving. Also, the measurement of the time-averaged maximum velocity is angle-dependent, and finding the correct angle may be difficult. We did not measure the umbilical vein diameter at a fixed distance from the placenta, and it is

shown that the umbilical vein diameter can show some variation with the distance from the placental insertion to the umbilicus.[28] An error in the diameter measurement may significantly impact the calculation of the volume blood flow. We calculated the umbilical vein diameter and velocity once only at the examinations. However, well-established methods of measurement were followed,[7] and our values of umbilical vein volume blood flow are in line with other studies. We have no reason to believe that possible erroneous measurements of umbilical vein volume blood flow were systematically related to fetal or placental size and thereby have biased our estimated correlations. The MRI measurements of the placental and fetal size have shown high reliability.[8] Any unsystematic imprecision of measurements tends to underestimate rather than overestimate associations.

## 5 | CONCLUSION

In this study, we found positive correlations of placental size and of placental–fetal ratio with umbilical vein volume blood flow in gestational week 37. We found no such correlations in gestational week 27. Further studies are needed to determine whether umbilical vein volume blood flow can be used to identify pregnancies with abnormal placental size relative to fetal size.

### AUTHOR CONTRIBUTIONS

Anne Eskild and Kari Flo designed the study; Anne Eskild, Kari Flo, Carl Petter Skaar Kulseng, and Helene Fjeldvik Peterson interpreted the results and prepared the tables and figures. Silje Sommerfelt recruited the participants, collected data, and performed the Doppler ultrasound examinations. Vigdis Hillestad collected and analyzed the MRI data. All authors contributed to writing the manuscript and the interpretation of the results.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### ETHICS STATEMENT

The Regional Committee for Medical Research Ethics, Norway (REK 2016/1185) and the data Protection Officer at Akershus University Hospital (ref. no 16-179, on 15 November 2016) approved the study. The women provided written consent for participation.

### ORCID

*Kari Flo* https://orcid.org/0009-0003-8103-5407
*Carl Petter Skaar Kulseng* https://orcid.org/0000-0002-8605-5402
*Helene Fjeldvik Peterson* https://orcid.org/0000-0002-4706-1885
*Vigdis Hillestad* https://orcid.org/0000-0001-5430-3398
*Anne Eskild* https://orcid.org/0000-0002-2756-1583

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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