OBSTETRICS

Number of episodes of reduced fetal movement at term: association with adverse perinatal outcome

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OBJECTIVE: The aims of this study were evaluation of the association of reduced fetal movements (RFM) and small-for-gestational-age (SGA) birth at term and to explore if fetal and maternal outcomes are different with single vs repeated episodes of RFM and normal fetal assessment test results.

STUDY DESIGN: This was a retrospective cohort study of all singleton pregnancies referred for RFMs at a tertiary fetal medicine unit from January 2008 through September 2014. Ultrasound and Doppler indices were obtained from a computerized ultrasound database and pregnancy outcome was collected from hospital records.

RESULTS: Of the 21,944 women with a singleton pregnancy booked for maternity care during the study period, 1234 women (5.62%) reported RFMs >36+0 weeks. Of these, 1029 women (83.4%) reported a single episode of RFM and 205 (16.6%) had ≥2

presentations for RFM. Women with repeated RFMs had a significantly higher mean uterine artery pulsatility index in the second trimester. The prevalence of SGA baby at birth in women presenting with a single episode as compared to repeated episodes of RFM was 9.8% and 44.2%, respectively (odds ratio, 7.3; 95% confidence interval, 5.1–10.4; $P < .05$).

CONCLUSION: Repeated episodes of RFMs at term are more likely to occur in women with high second-trimester uterine artery Doppler resistance indices and are strongly associated with the birth of SGA infants. Women presenting with repeated episodes of RFM should be treated as being at high risk of placental dysfunction irrespective of the results of prenatal ultrasound and Doppler assessment.

Key words: maternal outcomes, newborn outcomes, reduced fetal movements, small gestational age, uterine artery Doppler

Reduced fetal movements (RFM) are an important and frequently seen problem in maternity care, with 6-15% of women reporting at least 1 episode of RFM during the third trimester of pregnancy.[1,2] RFM, defined as a subjective perception of significantly reduced or absent fetal activity, is emerging as an important clinical marker to identify women with high risk of stillbirth and fetal growth restriction due to placental

dysfunction.[3] In fact, the majority of stillbirths seem to be preceded by a period of RFM for 3-4 days and 55% of women who have had stillbirth experience RFMs before fetal demise.[4-7] Recently it has been shown that women with RFMs have abnormal placental morphology and function, suggesting a potential association between placental insufficiency and presence of RFMs.[8,9] Several recent studies have reported that uterine artery (UtA) Doppler indices and pregnancy-associated plasma protein (PAPP)-A, both related to poor trophoblast development,[10] are associated with placenta-related complications such as preeclampsia, intrauterine growth restriction, and stillbirth.[11-17]

Assessment of women presenting with RFM is directed at identification of small fetuses due to placental dysfunction. Although women found to have normally grown fetuses are reassured, some of them will present with another episode of RFM despite normal results of

tests of fetal well-being. The aims of this study were evaluation of the association of RFM and small-for-gestational-age (SGA) fetuses at term and to explore if the fetal and maternal outcomes are different in the cohort of women with repeated RFM and normal fetal assessment test results.

MATERIALS AND METHODS

This was a retrospective cohort study of all singleton pregnancies referred for RFMs at a tertiary fetal medicine unit from January 2008 through September 2014. Part of this population, from 2008 through 2012, was reported in a previous study.[8] Pregnancies were dated by measurements of crown-rump length in the first trimester according to the national guidelines.[18] PAPP-A levels were measured at the time of routine 11-14 weeks' first-trimester combined screening test for Down syndrome. UtA Doppler indices were measured at the time of routine

TABLE 1
Comparison between women with 1 or repeated episodes of reduced fetal movements at term

Demographic	Total (n = 1234)	1 RFM episode (n = 1029)	Repeated RFM (n = 205)	Significance between 1 and repeated RFMs
Maternal age	29.9 (±5.5)	30.0 (±5.5)	29.4 (±5.7)	.171
BMI	25.31 (±5.3)	25.2 (±5.2)	25.8 (±5.8)	.147
Caucasian	786 (63.9%)	670 (65.9%)	116 (57.7%)	< .05
Afro-Caribbean	189 (15.3%)	156 (15.4%)	33 (16.4%)	.704
Asian	296 (23.9%)	240 (23.6%)	56 (27.9%)	.201
Other	11 (0.9%)	8 (0.8%)	3 (1.5%)	.334
Nulliparous	704 (57.0%)	582 (57.0%)	122 (59.5%)	.116
First- and second-trimester variables				
PAPP-A MoM	1.18 (0.7–1.42)	1.15 (0.69–1.41)	1.32 (0.70–1.46)	.583
BhCG MoM	1.20 (0.65–1.47)	1.22 (0.65–1.47)	1.10 (0.64–1.37)	.131
Mean UtA PI	0.89 (±0.42)	0.87 (±0.26)	0.98 (±0.27)	< .05
Scan assessment at RFM presentation				
Gestational age first episode of RFM	38.5 (36.6–40.2)	39.0 (37.3–40.2)	36.3 (33.5–38.6)	< .05
EFW first episode of RFM	3240 (±640)	3374 (±480)	2567 (±874)	< .05
EFW centile first episode of RFM	55.76 (34.5–75.4)	57.5 (37.0–76.3)	40.1 (19.8–65.8)	< .05
Suspected SGA first episode of RFM	37 (2.9%)	21 (2.0%)	16 (7.8%)	< .05
Outcome at birth				
Gestational age delivery	40.3 (39.3–41.2)	40.4 (39.4–41.2)	40.1 (39.1–41.1)	.479
Birthweight	3367 (±508)	3418 (±465)	3113 (±622)	< .05
Birthweight centile	39.7 (19.0–67.0)	41.5 (21.4–70.6)	15.9 (3.9–53.9)	< .05
SGA	184 (15.6%)	96 (9.8%)	88 (44.2%)	< .05
SGA with EFW >10th centile	153 (12.8%)	81 (8.4%)	72 (39.3%)	< .05
Birthweight of babies with EFW >10th centile	3262 (±636)	3435 (±451)	3161 (±624)	< .05
5-min Apgar <7	19 (1.6%)	11 (1.1%)	8 (4.0%)	< .05
Stillbirths	8 (0.6%)	6 (0.6%)	2 (1.4%)	.453

Data are shown as median (±interquartile range) or number (%).

BhCG, beta human chorionic gonadotropin; *BMI*, body mass index; *EFW*, estimated fetal weight; *MoM*, multiple of median; *PAPP*, pregnancy-associated plasma protein; *PI*, pulsatility index; *RFM*, reduced fetal movements; *SGA*, small for gestational age; *UtA*, uterine artery.

Scala. RFMs and adverse outcome at term. Am J Obstet Gynecol 2015.

anomaly scan between 19-23 weeks of gestation in nulliparous and high-risk parous women. UtA Doppler assessment was performed transabdominally as previously described.[19] Pulsatility index (PI) of the left and the right UtA was averaged to compute mean PI and plotted against a published reference range.[19] Women with UtA PI >90th centile at the second-trimester scan were offered growth scans at 28 and 36 weeks of gestation, counseled regarding the increased risk of preeclampsia, and asked to self-refer if they developed characteristic symptoms of the disorder. Low-dose aspirin for prevention of preeclampsia was not used routinely during the study period. Seven experienced operators with >5 years' experience in obstetric ultrasound and Doppler assessment performed all the scans. Ultrasound assessments were performed using GE Voluson E8 (GE Healthcare, Zipf, Austria). Maternal characteristics, including age, body mass index (BMI), and ethnic origin, were recorded during the first visit and the outcomes of pregnancies were collected.

Women presenting 1 or >1 episode of RFM during the study period were evaluated in the fetal day assessment unit. Those presenting with RFM ≥28 weeks underwent assessment of fetal well-being. The primary reason for the fetal assessment was the first or repeated episode of RFM. Electronic fetal heart rate (computerized cardiotocography) monitoring

TABLE 2

Comparison between pregnant women with AGA and SGA babies at term

Demographic	Total (n = 1234)	AGA (n = 1050)	SGA (n = 184)	Significance between AGA and SGA
Maternal age	30.0 ($\pm$5.5)	30.5 ($\pm$5.4)	29.0 ($\pm$5.9)	< .05
BMI	25.31 ($\pm$5.3)	25.5 ($\pm$5.3)	24.3 ($\pm$5.1)	< .05
Ethnicity				
Caucasian	751 (60.8%)	668 (67.9%)	83 (45.1%)	< .05
Afro-Caribbean	185 (14.9%)	158 (16.1%)	27 (14.7%)	.637
Asian	287 (23.2%)	207 (21.0%)	80 (43.5%)	< .05
Other	9 (0.7%)	7 (0.6%)	2 (1.0%)	.593
Nulliparous, n (%)	683 (55.3%)	565 (54%)	118 (64%)	.518
First- and second-trimester variables				
PAPP-A MoM	1.18 (0.7–1.42)	1.65 (0.74–1.43)	1.12 (0.60–1.54)	< .05
BhCG MoM	1.20 (0.6–1.47)	1.23 (0.65–1.48)	1.06 (0.64–1.29)	.144
Mean UtA PI	0.89 ($\pm$0.42)	0.86 ($\pm$0.24)	1.03 ($\pm$0.32)	< .05
Scan assessment at RFM presentation				
Gestational age first episode of RFM	38.5 (36.6–40.2)	38.6 (37.0–40.2)	37.5 (36.1–39.5)	< .05
EFW first episode of RFM	3240 ($\pm$640)	3342 ($\pm$590)	2672 ($\pm$592)	< .05
EFW centile first episode of RFM	55.7 (34.5–75.4)	60.9 (42.6–77.5)	20.0 (11.8–35.1)	< .05
Outcome at birth				
Gestational age delivery	40.4 (39.4–41.2)	40.5 (39.4–41.2)	38.6 (38.5–41.0)	< .05
Birthweight	3367 ($\pm$508)	3497 ($\pm$425)	2660 ($\pm$296)	< .05
Birthweight centile	39.7 (19.0–67.0)	50.5 ($\pm$26)	4.7 (2.7–7.1)	< .05
5 min Apgar <7	19 (1.5%)	10 (1.0%)	9 (4.9%)	< .05

Data are shown as median (interquartile range) or as number (%).

AGA, appropriate for gestational age; *BhCG*, beta human chorionic gonadotropin; *BMI*, body mass index; *EFW*, estimated fetal weight; *MoM*, multiple of median; *PAPP*, pregnancy-associated plasma protein; *PI*, pulsatility index; *RFM*, reduced fetal movements; *SGA*, small for gestational age; *UtA*, uterine artery.

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was performed until the Dawes-Redman criteria were met[20] and an ultrasound fetal evaluation of biometry, liquor volume, and fetal Doppler were performed. No follow-up was arranged if computerized cardiotocography, ultrasound, and Doppler assessment were noted as normal. Delivery or follow-up scans were arranged as appropriate for any suboptimal assessments. SGA was defined as birthweight (BW) <10th centile for gestational age. Pregnancies with major structural abnormalities, aneuploidy, or multiple gestations were excluded.

Statistical analysis

Data distribution was assessed according to the Kolmogorov-Smirnov test of normality. Data were expressed as mean (SD), or median and interquartile range. Categorical variables were described as number (%). The correlation between continuous variables was assessed by Pearson coefficient or by Spearman rho. Pearson χ^2 test was used to analyze categorical variables. Independent t test and Mann-Whitney test were used to compare continuous variables as appropriate. UtA mean PI centiles and BW centiles and z-scores were calculated from the appropriate reference ranges.[18] UtA mean PI was corrected for gestational age and multiple of medians were calculated on the reference ranges from the published centiles.[18] Logistic regression analysis was used to assess the association

of maternal characteristics, first- and second-trimester markers, and fetal outcomes for women with 1 or >1 episode of RFM and SGA; $P < .05$ was considered statistically significant. All P values were 2-tailed. Statistical analysis was performed using statistical software (SPSS 20.0; SPSS Inc, Chicago, IL).

RESULTS

The demographic and pregnancy characteristics of the cohorts presenting with 1 or >1 episode of RFM and SGA babies >36 weeks of gestation are presented in Tables 1 and 2. During the study period, 21,944 women with singleton pregnancies were booked for routine antenatal care in the department. There were 1234

TABLE 3
Indication for induction of labor

Indication, n = 473	n (%)
RFM	110 (23.2)
SGA	44 (9.3)
Prelabor rupture of membranes	28 (5.9)
Pregnancy-induced hypertension	37 (7.8)
Preeclampsia	13 (2.7)
Suboptimal fetal assessment by amniotic fluid, cCTG	16 (3.3)
Maternal disease, eg: chronic hypertension, diabetes, pregnancy cholestasis	24 (5.0)
Others	5 (1.0)
Missing data	6 (1.2)

cCTG, computerized cardiotocography; *RFM*, reduced fetal movements; *SGA*, small for gestational age.

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women (5.6%) who reported RFMs at term: 1029 women with a single episode of RFM and 205 with repeated (≥2) episodes of RFM (Table 1). Of 1234 patients with RFMs, 473 (38.3%) had induction of labor (IOL) at term. The indications of delivery are presented in Table 3.

The prevalence of SGA fetuses at the time of first episode of RFM calculated from the ultrasound estimated fetal weight centiles was significantly different for women presenting with single (2.0%) vs repeated (7.8%, $P < .05$) RFMs. The overall prevalence of SGA at birth in the cohort of patients with and without RFMs was 15.6% (184/1182) and 7.3% (1601/21,944), respectively. The prevalence of SGA birth in women presenting with a single or repeated episodes of RFM was 9.8% (96/983) and 44.2% (88/199), respectively (odds ratio [OR], 7.3; 95% confidence interval, 5.1–10.4; $P < .05$ between the 2 groups).

Compared to women with a single episode of RFM, those presenting with repeated RFM had higher midpregnancy UtA Doppler PI and gave birth to babies with lower 5-minute Apgar scores. In the cohort of women presenting with RFM, women of Caucasian ethnicity were less likely to represent with repeated RFMs than those of Asian or Afro-Caribbean ethnicity. Compared to women who gave birth to appropriate-for-gestational-age

babies, the cohort of women with SGA babies were more likely to be younger, to have a lower BMI, and to be of Asian ethnicity and had higher midpregnancy UtA Doppler indices. No significant correlation was seen between SGA birth at term and first-trimester PAPP-A levels in this cohort.

Logistic regression analysis to assess the relation between maternal and pregnancy characteristics with SGA and repeated episode of RFM are shown in Table 4. Midpregnancy UtA Doppler PI was the only ultrasound parameter significantly associated with both SGA and repeated episodes of RFM at term. Logistic regression analysis demonstrated no significant associations between first-trimester PAPP-A levels, BMI, or ethnicity with either RFMs or SGA at term.

COMMENT
Main findings
The findings in this study demonstrate that higher mean UtA PI at midgestation is associated with repeated episodes at term of RFM and the subsequent birth of a small baby. At the time of the first episode of RFM, the incidence of fetal SGA diagnosis was significantly higher in the cohort of patients with repeated episode of RFM, but the prevalence of SGA is further increased at birth in this group, from 7.8-44.2% ($P < .05$). The prevalence of SGA infants was higher in

the group of women with repeated RFM compared to those reporting only 1 episode of RFM. Furthermore, exclusion of fetuses found to be small at the first presentation did not change the significantly lower BW centile and a higher prevalence of SGA infants at term. Second-trimester UtA PI, a known marker for impaired placentation, was independently associated with the occurrence of repeated episode of RFM at term. After adjusting the results for potential confounding variables, logistic regression analysis demonstrated that second-trimester UtA PI was the only independent marker for both SGA and repeated episodes of RFM >36 weeks' gestation. The study results strongly suggest that the presence of repeated episodes of RFM increase the risk of having a SGA infant despite normal fetal assessment test results. Furthermore, they support a potential causative relation between impaired placentation and subsequent development of both RFM and SGA at term.

Interpretation
In this study, conventional risk factors for placental insufficiency such as BMI and Afro-Caribbean ethnicity showed only a weak correlation with repeated RFM at term when adjusted for PAPP-A, UtA Doppler, and other confounding variables. When assessed in isolation, BMI and PAPP-A levels were not associated with an increased risk of repeated episodes of RFM at term. It has been estimated that approximately 6-10% of women during the third trimester referred at least 1 episode of RFM.[2,9,21-26] The prevalence in the current study was 7.5%. This is in keeping with the findings reported by Frøen et al.[2,6,27] There have been previous reports that women reporting RFM have altered placental structure and function. Increased infarction, increased density of syncytial knots, reduced vascularity, trophoblast area, and nutrients exchange activity has been reported in the placenta of women with RFM.[9] These placental characteristics are similar to those observed in pregnancies complicated by SGA, suggesting a causal relationship among placental insufficiency, fetal growth restriction, and the

presence of RFMs. Moreover, this study has shown a strong correlation between UtA Doppler PI and the presence of repeated RFM as well as birth of a small fetus, suggesting that high UtA Doppler indices in the second trimester increase the risk of both SGA and RFMs (OR, 4.3 for RFM; and OR, 5.7 for SGA). We, as well as other researchers, have previously demonstrated that second-trimester UtA PI is more strongly associated with stillbirth than the other conventional risk factors.[27]

Strength and limitation

A large number of participants has led to robust estimation of OR. We have adjusted for maternal characteristics and UtA Doppler indices in the second trimester. Retrospective design is an obvious limitation, but we have conducted a subanalysis after excluding those fetuses known to be small at initial presentation. UtA Doppler screen is offered to nulliparous and high-risk parous women at our center. We explain the relevance of this finding to those with a positive UtA Doppler screen (mean UtA PI of ≥90th centile). They are informed about the increased risks of preeclampsia, placental dysfunction, and stillbirth, and the need for surveillance. It is possible that these women were keener to look out for and report RFM. However, in our cohort the overall prevalence of UtA mean PI >90th centile was comparable to the overall prevalence in the normal population of pregnancies without RFMs,[28] suggesting this bias not to be a significant one. Similarly, prenatal identification of an SGA fetus is unlikely to bias our findings because the rate of SGA diagnosed at the time of first episode of RFM was lower compared to the percentage of SGA infants at term in both groups.

Conclusion

The current data support the assertion that repeated RFM at term is strongly associated with SGA infants. Women presenting with repeated episodes of RFM should be treated as being at high risk of placental dysfunction irrespective of the results of the ultrasound scan. A large prospective study is underway to assess the effectiveness of fetal

assessment and possible IOL to prevent stillbirth.[29] The study suggests that IOL for repeat presentation with RFM at term may be a reasonable management strategy. The role of UtA Doppler indices as markers in stratification of risk of women presenting with repeated episode of RFM and SGA birth should be ascertained in a prospective study. ∎

TABLE 4
Logistic regression analysis for prediction of repeated episode of RFM and SGA at term

Variable	OR	95% CI	P value
Repeated RFM (n = 205)			
Maternal age	0.973	0.934–1.014	.189
Ethnicity			
Caucasian	0.621	0.152–2.547	.509
Afro-Caribbean	0.742	0.231–2.392	.618
Asian	0.802	0.217–2.960	.741
BMI	1.013	0.970–1.057	.567
PAPP-A (MoM)	1.041	0.880–1.232	.637
UtA mean PI (second trimester)	4.300	2.003–9.232	< .05
EFW <10th centile	3.133	1.111–8.833	< .05
SGA (n = 184)			
Maternal age	0.973	0.929–1.020	.258
Ethnicity			
Caucasian	0.285	0.060–1.354	.114
Afro-Caribbean	0.378	0.115–1.241	.109
Asian	1.473	0.341–6.368	.604
BMI	0.959	0.907–1.015	.150
PAPP-A (MoM)	1.036	0.873–1.229	.684
UtA mean PI (second trimester)	5.730	2.422–13.556	< .05
Repeated RFM	8.041	4.627–13.976	< .05

Values adjusted for other confounding variables (maternal age, BMI, ethnicity).

BMI, body mass index; *CI*, confidence interval; *EFW*, estimated fetal weight; *MoM*, multiple of median; *OR*, odds ratio; *PAPP*, pregnancy-associated plasma protein; *PI*, pulsatility index; *RFM*, reduced fetal movements; *SGA*, small for gestational age; *UtA*, uterine artery.

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