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Duration of sexual relationship and its effect on preeclampsia and small for gestational age perinatal outcome

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Abstract

The aim of this study was to determine if women with preeclampsia or delivering small for gestational age (SGA) babies are more likely to have a short duration of sexual relationship compared with those who have uncomplicated pregnancies. In a prospective cohort study, 2507 nulliparous women with singleton pregnancies were interviewed at 15 ± 1 weeks gestation about the duration of their sexual relationship with the biological father. Short duration of sexual relationship (≤6 months, ≤3 months, or first intercourse) was compared between women with preeclampsia ($N = 131$) or SGA babies ($N = 263$) and those with uncomplicated pregnancies ($N = 1462$). Short duration of sexual relationship was more common in women with preeclampsia compared with uncomplicated pregnancies (≤6 months 14.5% versus 6.9%, adjusted odds ratio [adjOR] 1.88, 95% CI 1.05–3.36; ≤3 months 6.9% versus 2.5%, adjOR 2.32, 95% CI 1.03–5.25; first intercourse 1.5% versus 0.5%, adjOR 5.75, 95% CI 1.13–29.3). Although the total number of semen exposures was lower in SGA, SGA was not associated with a shorter duration of sexual relationship. On post hoc analysis, the subgroup of SGA with abnormal uterine artery Doppler at 20 weeks ($N = 58$) were more likely to have had a short sexual relationship compared with controls (≤6 months adjOR 2.33, 95% CI 1.09–4.98; ≤3 months adjOR 3.22, 95% CI 1.18–8.79; first intercourse adjOR 8.02, 95% CI 1.58–40.7). We conclude that compared to uncomplicated pregnancies, short duration of sexual relationship is more common in women who develop preeclampsia and women with abnormal uterine artery Doppler waveforms who deliver an SGA baby.

Keywords: Duration of sexual relationship; Preeclampsia; Small for gestational age; Sperm; Semen exposure

1. Introduction

Several epidemiological studies support the concept of maternal–fetal (paternal) immune maladaptation being centrally implicated in the causation of preeclampsia. The 'Immune Maladaptation Hypothesis' postulates that an inappropriate maternal immune response towards

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foreign fetal antigens derived from proteins encoded by the father's DNA plays a key role in the pathogenesis of preeclampsia (Sibai et al., 2005). It is proposed that this abnormal immune response contributes to restricted trophoblast invasion of spiral arteries, a characteristic feature of preeclampsia and also, to some extent, small for gestational age (SGA) pregnancies (Khong et al., 1986).

Marti and Herrmann (1977) were the first to suggest that repeated exposure to semen from the biological father of the baby reduces the risk of preeclampsia. Robillard et al. (1994) published a retrospective study on the relationship between duration of cohabitation and pregnancy-induced hypertension, which included both preeclampsia and gestational hypertension. They found that length of sexual cohabitation before conception was inversely related to the incidence of pregnancy-induced hypertension. Although most subsequent retrospective studies concurred with this finding (Dekker and Robillard, 2007), a recent large prospective study in women of mixed parity found no association between duration of sexual relationship with the biological father and the risk of preeclampsia (Ness et al., 2004). Thus it remains uncertain whether a short duration of sexual relationship prior to conception is associated with preeclampsia. Further, despite the overlap in placental pathology underlying preeclampsia and SGA, the relationship between duration of sexual relationship and SGA pregnancies has never been investigated.

This persisting controversy led us to design the current study to estimate whether short duration of sexual relationship in nulliparous women is associated with a higher risk of developing preeclampsia or SGA. We hypothesised that women who develop preeclampsia or deliver an SGA infant are more likely to have had a short duration of sexual relationship with the biological father and/or a lower total number of semen exposures compared with women who had an uncomplicated pregnancy.

2. Materials and methods

Between November 2004 and July 2007, healthy nulliparous women with singleton pregnancies were recruited into a prospective, cohort study (Screening for Pregnancy Endpoints, SCOPE study) in Auckland, New Zealand and Adelaide, Australia (ACTRN12607000551493, Australian and New Zealand Clinical Trials Registry). Ethical approval for SCOPE was obtained from local ethics committees (New Zealand AKX/02/00/364 and Australia 1712/5/2008), and all women provided written consent. In the current study, we investigated the duration of sexual relationship prior to conception with the biological father in women who later developed preeclampsia or delivered an SGA baby compared with all those who had an uncomplicated pregnancy in the cohort.

SCOPE study participants were referred from hospital antenatal clinics, obstetricians, general practitioners, community midwives and by self-referral. Women considered at high risk of preeclampsia, SGA or spontaneous preterm birth because of underlying medical conditions or gynaecological history, including three or more miscarriages and those who received interventions that may modify main outcomes were excluded. Women with multiple partners who were unsure of the identity of the biological father of the baby were also excluded from the current study. Participants were interviewed at 15 ± 1 weeks and 20 ± 1 weeks gestation by SCOPE research midwives, then tracked throughout pregnancy and information on pregnancy outcome was usually collected within 72 h of birth.

At the 15 ± 1 weeks interview, maternal age, ethnicity (self-assigned), gravidity, smoking status, blood pressure, height and weight were recorded. Details about the pre-pregnancy sexual history with the biological father of the index pregnancy were collated, including conception following the first episode of sexual intercourse, months of sexual relationship and cumulative months of condom or diaphragm use during this relationship. Months of sexual relationship without barrier were calculated by deducting months of barrier use from total months of the sexual relationship. Total semen exposure, a measure of exposure to paternal antigens, was estimated by multiplying the months of sexual relationship without barrier and the frequency of sexual intercourse with the biological father per month, in the 3 months prior to conception. Information about oral sex was not collected. The duration of sexual relationship was then categorised as a sexual relationship of $\leq$6 months, $\leq$3 months or conceived after first sexual intercourse with the biological father of the baby.

Uterine artery Doppler ultrasound was performed at 20 ± 1 weeks gestation in accordance with a standard operating procedures manual. The angle of insonation was $<50^{\circ}$ and a minimum of five waveforms recorded. In-built software calculated the resistance index (RI) for both uterine arteries. Mean RI was calculated from the right and left uterine arteries. If only a left or right uterine RI result was available, this was used as the 'mean RI'. An abnormal uterine artery Doppler was defined as a mean resistance index >90th centile at 20 ± 1 weeks' gestation for the cohort (Groom et al., 2009).

The primary outcomes were preeclampsia and SGA infants. Gestational hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg developing after 20 weeks gestation (but before the onset of labour) or in the postnatal period. Preeclampsia was gestational hypertension with proteinuria (24 h urinary protein ≥300 mg or spot urine protein:creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥2+) or any multi-organ complication of preeclampsia (Brown et al., 2000). Multi-organ complications included any of the following: acute renal insufficiency, liver dysfunction or rupture, eclampsia, imminent eclampsia or cerebral haemorrhage, thrombocytopenia, disseminated intravascular coagulation or haemolysis. Small for gestational age was defined as birthweight <10th customised birthweight centile (www.gestation.net) (Gardosi, 2007). Gestational hypertension was investigated as a secondary outcome. Controls had an uncomplicated pregnancy defined as a pregnancy with no antenatal obstetric or medical complications resulting in delivery of an appropriately grown, healthy baby at or beyond 37 weeks gestation.

3. Statistical methods

Statistical analysis was performed using SAS® system 9.1. For continuous variables the data for each endpoint (preeclampsia or SGA) were compared to the uncomplicated pregnancy group, using either a two-sample Student's *t*-test, or the Wilcoxon rank sum test, according to whether or not the data were normally distributed. For categorical variables Chi-square was used to investigate the association with each endpoint. R version 2.8.0 (cran.r-project.org) was used to fit logistic regression models to each of the endpoints (preeclampsia or SGA versus controls), with the regression coefficients used to provide estimates of odds ratios for each of the measures of variable of interest. For each variable adjusted odds ratios (adjOR) were also calculated by adding the following variables to the logistic regression model: maternal age, ethnicity, primigravidity, BMI, mean arterial blood pressure and smoking status at 15 ± 1 weeks' gestation. Complete data were available for all variables used in this analysis.

A prospective power calculation was not performed for this study as a fixed number of SCOPE participants

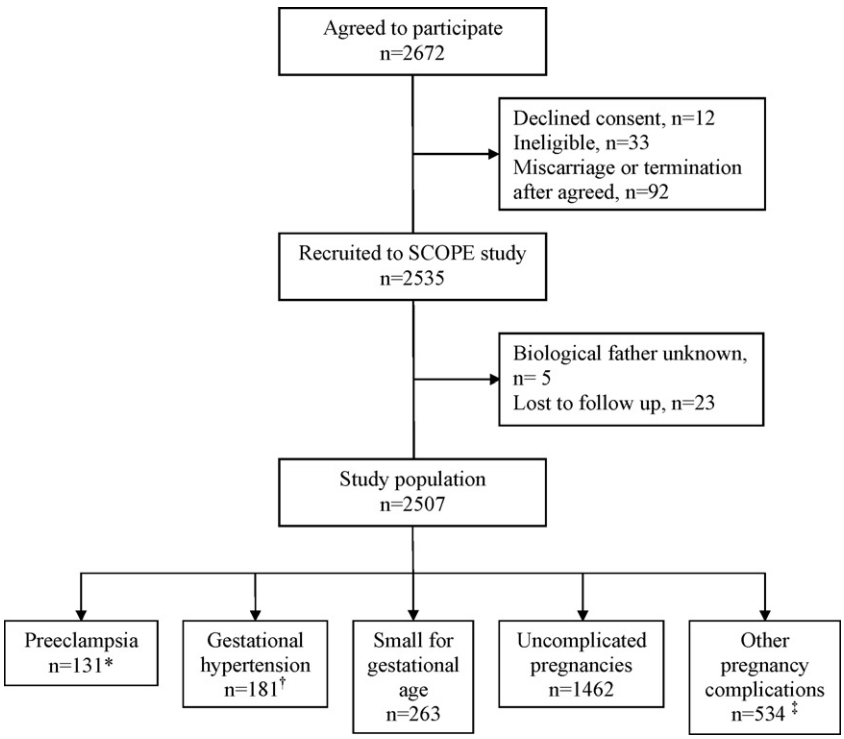

Fig. 1. Recruitment flow chart. *Includes 29 with preeclampsia and small for gestational age. †Includes 35 with gestational hypertension and small for gestational age. ‡Spontaneous preterm birth, gestational diabetes, antepartum haemorrhage, admission to hospital for other significant medical or surgical conditions, chromosomal abnormalities and congenital anomalies.

Table 1
Maternal characteristics.

	Controls ($N=1462$)	Preeclampsia ($N=131$)	P-value*	SGA ($N=263$)	P-value†
Age (y)	28.8 (5.5)	27.2 (6.0)	0.001	28.8 (6.0)	0.96
Ethnicity			0.67		0.19
European	1273 (87.1)	113 (86.3)		223 (84.8)	
Polynesian	60 (4.1)	7 (5.3)		10 (3.8)	
Asian	75 (5.1)	4 (3.1)		12 (4.6)	
Indian	31 (2.1)	4 (3.1)		9 (3.4)	
Other	23 (1.6)	3 (2.3)		9 (3.4)	
Gravidity			0.64		0.02
1	1115 (76.3)	101 (77.1)		180 (68.4)	
2	263 (18.0)	25 (19.1)		67 (25.5)	
≥3	84 (5.8)	5 (3.8)		16 (6.1)	
At 15 ± 1 weeks					
Smoking	110 (7.5)	16 (12.2)	0.06	42 (16.0)	<0.0001
Body mass index	24.6 (4.2)	28.1 (6.9)	<0.0001	25.9 (6.0)	0.001
Systolic blood pressure	106 (11)	115 (12)	<0.0001	109 (11)	<0.0001
Diastolic blood pressure	64 (8)	70 (9)	<0.0001	66 (9)	0.0004
Pregnancy outcome					
Maximum systolic blood pressure	118 (10)	157 (14)	<0.0001	128 (18)	<0.0001
Maximum diastolic blood pressure	72 (8)	101 (10)	<0.0001	80 (14)	<0.0001
Gestation at delivery (wks)	40.0 (1.2)	37.8 (2.6)	<0.0001	38.4 (4.1)	<0.0001
Birthweight (g)	3588 (402)	3027 (778)	<0.0001	2539 (630)	<0.0001
Birthweight centile	55 (25)	44 (32)	0.0004	5 (3)	<0.0001

Results are expressed as mean (SD) or N (%).
* Preeclampsia versus controls.
† SGA versus controls.

were available for study ($N=2507$). A retrospective power analysis demonstrated that we had 98% power to detect a two-fold increase in risk of preeclampsia in those with sexual relationship of ≤6 months duration.

4. Results

Of 2535 pregnant women recruited, follow-up was complete in over 99% (Fig. 1). Amongst the 2507 women eligible for the study, 131 (5.2%) developed preeclampsia, 181 (7.2%) had gestational hypertension, 263 (10.5%) had SGA babies and 1462 (58%) women had uncomplicated pregnancies. Twenty-nine women (1.2%) had both preeclampsia and an SGA baby. Amongst 131 women with preeclampsia, 115 (88%) had proteinuria and the remainder 16 (12%) were diagnosed as they had multi-organ complications of preeclampsia. In total 53 (40%) women with preeclampsia developed multi-organ complications.

Maternal characteristics and pregnancy outcomes are shown in Table 1. Barrier contraception was used during the relationship with the biological father of the index pregnancy by 64.1% of women with preeclampsia (84 of 131), 63.9% of women with an SGA baby (168 of 263) and 68.6% of women with uncomplicated pregnancies (1003 of 1462).

Women who developed preeclampsia had a shorter duration of sexual relationship than controls (Table 2). Compared with controls, women with preeclampsia were twice as likely to have a sexual relationship of ≤3 months (adjOR 2.32, 95% CI 1.03–5.25) and ≤6 months (adjOR 1.88, 95% CI 1.05–3.36). The results were similar when we examined the duration of sexual intercourse without barrier contraception (Table 2). Women with gestational hypertension ($N=181$) were not more likely to have a short duration of sexual relationship compared to women with uncomplicated pregnancies (≤6 months: 19 [10.5%] versus 101 [6.9%], adjOR 1.36, 95% CI 0.75–2.44; ≤3 months: 7 [3.9%] versus 37 [2.5%], adjOR 1.33, 95% CI 0.53–3.34).

Amongst women who delivered an SGA infant, the duration of sexual relationship without using barrier contraception was shorter and estimated total semen exposure was less than that in women with uncomplicated pregnancies (Table 3). However, after adjusting for potential confounders, SGA pregnancies were not associated with a short duration of sexual relationship (with or without barrier contraception). To further explore

Table 2
Duration of sexual relationship and preeclampsia.

	Preeclampsia ($N=131$)	Controls ($N=1462$)	OR (95% CI) or P-value	AdjOR (95% CI)*
Months of sexual relationship	40 (18–78)	48 (24–84)	0.03	
≤3 months	9 (6.9)	37 (2.5)	2.84 (1.34–6.02)	2.32 (1.03–5.25)
≤6 months	19 (14.5)	101 (6.9)	2.29 (1.35–3.87)	1.88 (1.05–3.36)
Months of sexual relationship without barrier contraception	29 (6–54)	36 (12–66)	0.02	
≤3 months	24 (18.3)	163 (11.2)	1.79 (1.12–2.86)	1.69 (1.02–2.80)
≤6 months	38 (29.0)	264 (18.1)	1.85 (1.24–2.77)	1.69 (1.10–2.62)
Conceived on first intercourse	2 (1.5)	7 (0.5)	3.22 (0.66–15.7)	5.75 (1.13–29.3)
Sexual intercourse per month†	12 (8–20)	12 (7–15)	0.30	
Semen exposure‡	276 (75–576)	336 (120–672)	0.14	

Results are expressed as median (interquartile range) or N (%).
* Adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status.
† In 3 months prior to conception.
‡ Total number of sexual intercourse without barrier contraception with biological father of baby.

the relationship between SGA and semen exposure we performed a post hoc analysis in the SGA subgroup with an abnormal uterine artery Doppler waveform, a surrogate marker for reduced utero-placental perfusion. Women with an SGA baby associated with abnormal uterine artery Doppler ($N=58$) were more likely to have a sexual relationship of ≤6 months (adjOR 3.22, 95% CI 1.18–8.79) or ≤3 months (adjOR 2.33, 95% CI 1.09–4.98) compared with those with uncomplicated pregnancies (Table 4). Although small numbers, this SGA subgroup was eight times more likely to have conceived after the first episode of sexual intercourse with the father of the baby (adjOR 8.02, 95% CI 1.58–40.7) compared with the controls. None of the women in this subgroup of SGA with a sexual relationship of ≤6 months' duration also had preeclampsia.

5. Discussion

This large prospective multicentre study using high quality data demonstrates that a short duration of sexual relationship increases the risk of preeclampsia. Women

Table 3
Duration of sexual relationship and SGA infants.

	SGA $N=263$	Controls $N=1462$	OR (95% CI) or P-value	AdjOR (95% CI)*
Months of sexual relationship	42 (20–84)	48 (24–84)	0.06	
≤3 months	10 (3.8)	37 (2.5)	1.52 (0.75–3.10)	1.51 (0.73–3.12)
≤6 months	29 (11.0)	101 (6.9)	1.67 (1.08–2.58)	1.55 (0.98–2.46)
Months of sexual relationship without barrier contraception	30 (8–60)	36 (12–66)	0.03	
≤3 months	38 (14.5)	163 (11.2)	1.35 (0.92–1.97)	1.39 (0.94–2.05)
≤6 months	57 (21.7)	264 (18.1)	1.26 (0.91–1.73)	1.27 (0.91–1.76)
Conceived on first intercourse	3 (1.4)	7 (0.5)	2.40 (0.62–9.33)	2.42 (0.62–9.48)
Sexual intercourse per month†	10 (6–16)	12 (7–15)	0.70	
Semen exposure‡	240 (92–576)	336 (120–672)	0.02	

Results are expressed as median (interquartile range) or N (%).
* Adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status.
† In 3 months prior to conception.
‡ Total number of sexual intercourse without barrier contraception with biological father of baby.

Table 4
Duration of sexual relationship and SGA with abnormal uterine Doppler.

	SGA with abnormal uterine RI $N = 58$	Controls $N = 1462$	OR (95% CI) or P-value	AdjOR (95% CI)*
Months of sexual relationship	36 (9–85)	48 (24–84)	0.10	
≤3 months	5 (8.6)	37 (2.5)	3.63 (1.37–9.62)	3.22 (1.18–8.79)
≤6 months	10 (17.3)	101 (6.9)	2.81 (1.38–5.71)	2.33 (1.09–4.98)
Months of sexual relationship without barrier contraception	19 (6–72)	36 (12–66)	0.05	
≤3 months	10 (17.2)	163 (11.2)	1.66 (0.82–3.35)	1.60 (0.78–3.27)
≤6 months	15 (25.9)	264 (18.1)	1.58 (0.87–2.89)	1.45 (0.78–2.71)
Conceived on first intercourse	2 (3.5)	7 (0.5)	7.42 (1.51–36.5)	8.02 (1.58–40.7)
Sexual intercourse per month†	12 (6–16)	12 (7–15)	0.53	
Semen exposure‡	237 (76–504)	336 (120–672)	0.048	

Results are expressed as median (interquartile range) or N (%).
* Adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status.
† In 3 months prior to conception.
‡ Total number of sexual intercourse without barrier contraception with biological father of baby.

who developed preeclampsia were twice as likely to have had a short duration of sexual relationship as women with uncomplicated pregnancies. The relationship between short duration of sexual relationship and the overall risk of SGA was no longer significant after adjustment for confounding factors (≤6 months: adjOR 1.55, 95% CI 0.98–2.46).

Our results for preeclampsia are consistent with those of Robillard et al. (1994), but differ from a previous prospective study of 2211 women of mixed parity which reported the lowest quartile for 'time to conception' was not associated with an increased risk of preeclampsia. Ness et al. (2004) used a similar measure to our total duration of sexual relationship, but there were fundamental differences in study design (Ness et al., 2004). Barrier contraception was addressed by performing a stratified analysis for barrier and non-barrier users, rather than calculating the duration of sexual relationship without barrier. Multiparous women were included in their study, whereas our cohort comprised only nulliparous women. Multiparous women are less likely to develop preeclampsia than nullipara, and there is a complex interaction between changing of partners and the inter-pregnancy interval that were not addressed in the Ness study (Lie et al., 1998; Skjaerven et al., 2002).

The 'protective' effect of a more lengthy sexual relationship could be explained by so-called maternal mucosal tolerance to paternal antigens (Robertson et al., 2002). Deposition of semen in the female genital tract elicits a cascade of cellular and molecular events that resemble a classic inflammatory response. Peters et al. (2004) recently confirmed that semen exposure induces mucosal alloimmunisation in women. The cellular cytokine responses in human vaginal and cervical cells have recently been elucidated (Sharkey et al., 2007). Limited semen exposure is the most likely explanation for the high incidence of preeclampsia in teenagers. An important contributing factor may be seminal-vesicle-derived transforming growth factor β (TGFβ) which is present both as a soluble form at five times the concentration of that in blood (Nocera and Chu, 1995), as well as bound to sperm (Chu et al., 1996). TGFβ elicits strong type 2 and Th3 immune responses towards antigens present in semen (Robertson et al., 2002). The antigenic stimulus is likely to be conveyed by sperm (Wang et al., 2002), since the risk for preeclampsia was three times higher in women conceiving via intracytoplasmic sperm injection (ICSI) with surgically obtained sperm (from men with complete azoospermia) than in those with standard in vitro fertilisation and ICSI using sperm cells obtained by masturbation. Repeated intercourse with sustained antigen exposure in the appropriate cytokine environment mediated by TGFβ is now thought to be essential in this partner-specific mucosal tolerance (Robertson et al., 2002).

By initiating a type 2 or T regulatory cell dominated immune response towards paternal antigens, seminal TGFβ may inhibit the induction of type 1 responses against the semi-allogeneic conceptus that are thought to be associated with poor placental development and restricted fetal growth. Furthermore, T helper type 2 (Th2) and Th3 lymphocytes interact with

both placental trophoblasts and the maternal decidual vasculature to facilitate their remodelling (Leonard et al., 2006). Impaired spiral arterial remodelling reduces utero-placental perfusion and thereby predisposes to preeclampsia and SGA (Khong et al., 1986).

All measurements of exposure to semen pre-conception have inherent limitations. It is not feasible to conduct a pre-conception study that prospectively collects information about semen exposure with the biological father. Many women are unlikely to know at the time of first semen exposure that this partner will ultimately be the father of a child. Once pregnant, the easiest variable to collect is 'total duration of sexual relationship' which is subject to less recall bias, but does not account for use of barrier contraception. Use of barrier contraception in women with a sexual relationship ≤6 months will have little impact on these data, as these women will still have a short duration of semen exposure. However, 'total duration of sexual relationship' fails to recognise the group with a long sexual relationship but a short duration of exposure to their partner's semen due to prolonged use of barrier contraception. Duration of sexual relationship without barrier contraception is generally thought to be a better measure of semen exposure. However, this variable (collected using the methods described above) at times fails to capture the overall time period between first exposure to the partner's semen and conception in certain situations, such as when an initial unprotected intercourse is followed by months of barrier contraception and then a period of unprotected intercourse leading to conception. The variable 'semen exposure' used herein provides a measure of total semen antigenic load but again, does not capture the time course. The timeline of exposure may be important in modulating the maternal immune response to paternal antigens. As we considered it difficult to collect reliable data on oral sex within the broader pregnancy screening study, this information was not available. We therefore cannot account for sperm exposure via this route (Koelman et al., 2000). Future studies could endeavour to measure this additional information.

Even though our study shows that a short sexual relationship doubles the risk of preeclampsia, the majority of women with a short sexual relationship (84%) still had uncomplicated pregnancies and 85% of women with preeclampsia did not have a sexual relationship of ≤6 months' duration. This emphasises the multi-factorial nature of this complex disease.

This is the first report to examine the relationship between the duration of sexual relationship and SGA infants. While an association was found between SGA and short duration of sexual relationship on univariate analysis, this effect was no longer significant after adjusting for potential confounders. The subgroup of SGA pregnancies with features of abnormal placentation as indicated by abnormal uterine artery Doppler studies might be expected to have higher rates of short duration of semen exposure. Our post hoc analysis found a two- to three-fold increase in short duration of sexual relationship in this subgroup of SGA pregnancies. Further exploration of this relationship requires more data from a larger cohort of SGA babies, with a priori hypotheses regarding the relationship between the length of sexual relationship and different SGA phenotypes.

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