The duration of sexual relationship and its effects on adverse pregnancy outcomes

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Abstract

This study aims to determine if a short duration of sexual relationship is more common among women who experience adverse pregnancy outcomes including gestational hypertension (GHT), preeclampsia, small for gestational age (SGA) pregnancies and spontaneous preterm birth (sPTB) with or without abnormal uterine artery Doppler compared to women who have uncomplicated pregnancies. 5591 nulliparous women from the Screening for Pregnancy Endpoints (SCOPE) study were included. The risk for pregnancy complications for women who had a duration of sexual relationship of ≤3 months, 4-6 months, 7-9 months, 10-12 months was compared with women who had a duration of sexual relationship of > 12 months. Uterine artery Doppler was performed at 20 ± 1 weeks' gestation. A short duration of sexual relationship (≤ 3 months) was more common among women with SGA in the presence of abnormal uterine artery Doppler [9.8% vs 3.0%, aOR (95% CI) 3.4 (1.6-7.08] compared to women who had uncomplicated pregnancies. A short duration of sexual relationship (≤ 3 months) was also more common among women who had abnormal uterine artery Doppler compared to those with normal uterine artery Doppler [6.1% vs 3.1%, aOR (95% CI) = 2.1 (1.4-3.2)]. A short duration of sexual relationship was not associated with preeclampsia after adjusting for confounders. A short duration of sexual relationship is more common among women who deliver SGA infants with features of placental insufficiency as indicated by abnormal uterine artery Doppler.

Keywords	duration of sexual relationship; preeclampsia; gestational hypertension; SGA; Uterine artery Doppler
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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

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The Editor in Chief
Journal of Reproductive Immunology

RE: The duration of sexual relationship and its effects on adverse pregnancy outcomes

Prabha Andraweera, Claire T Roberts, Shalem Leemaqz, Lesley McCowan, Jenny Myers, Louise C Kenny, James Walker, Lucilla Poston, Gus Dekker on behalf of the SCOPE Consortium

We wish to submit the above titled manuscript for consideration for publication in the "Journal of Reproductive Immunology".
The duration of exposure to paternal antigens in seminal fluid is known to induce maternal tolerance to the allogenic fetus and facilitate successful placentation. We aimed to determine if women with pregnancy outcomes including gestational hypertension (GHT), preeclampsia, small for gestational age (SGA) pregnancies and spontaneous preterm birth (sPTB) with or without abnormal uterine artery Doppler flow velocity waveforms at 20 weeks' gestation are more likely to have had a shorter duration of sexual relationship than those with uncomplicated pregnancies in this large SCOPE pregnancy cohort (n = 5591).

Our study demonstrates that compared with women who have uncomplicated pregnancies, a short duration of sexual relationship is more common among women who deliver SGA infants with features of placental insufficiency as indicated by abnormal uterine artery Doppler studies.

This manuscript has not previously been published and is not under review by any other journal. All authors meet the requirements for authorship as outlined in the "Journal of Reproductive Immunology".

Regards

Gustaaf Dekker

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Authors' response to reviewers

We thank the reviewers for their positive and constructive comments. We have made the suggested changes and believe it has made a substantial improvement to the manuscript and in particular made the story more complete. All changes are highlighted in the revised manuscript.

Comments from the editors and reviewers:
Reviewer 2

The authors have improved the manuscript by correcting misleading statements and providing further study documentation. Below are my remaining comments/suggestions in response to the author's responses:

***Overall Point #1**: While some women using barrier contraception may have been exposed to sperm for one week of the month during the "safe period"—these women were not exposed 75% of the time. This explanation does not justify the decision to not control for this variable given the established association of barrier contraception with risk of preeclampsia. Furthermore, as Kho et al. controlled for this variable and the present study findings for preeclampsia do not agree those found by Kho et al., this variable should be included in the present analysis.*

We have now corrected all results for use of barrier contraception as suggested by the reviewer.

***Methods Point #2: "**How is short duration of sexual cohabitation defined?" The author did not respond to this question. One might assume that sexual cohabitation of more than 12 months is not short (but of course this depends on the fertility goals and use of contraception). My point here is that if the author's stated objective is to "…determine the threshold of sufficient length of sexual cohabitation that would reduce risk for pregnancy complications", their current analysis using dichotomous categorizations of length of sexual cohabitation does not allow for identification of a threshold. I suggest that the author set up the analysis with a common referent group (e.g., >12 months of sexual cohabitation) and use finer categorizations of sexual cohabitation (e.g., 0-3 months, 4-6 months, 6-9 months, 10-12 months) to identify the duration of sexual cohabitation at which there is no further increased risk of the study outcomes relative to women with sexual cohabitation of >12 months. This*

analysis will provide results that are more informative and of greater interest to readers than those that are possible with their current analysis.

We have now re analysed all results as suggested by the reviewer. All results are presented with the >12 months group as the reference. The revised tables are highlighted.

Methods Point #3: *3. "Analysis of a dose-response relationship between duration of sexual cohabitation and pregnancy outcomes could strengthen the author's thesis that shorter cohabitation is associated with increasing risk of preeclampsia and the other outcomes. Such an analysis is certainly indicated."*

I commend the author for modeling the continuous association of months of sexual cohabitation with risk of preeclampsia, which clearly shows that risk decreases as duration of cohabitation increases. While the categorical analysis suggested above is less sophisticated, it addresses the author's goal of identifying the trend in risk of adverse pregnancy outcomes associated with increasing duration of sexual cohabitation.

We agree with the reviewer and have included these plots in figures 2 and 3 of the revised manuscript

Methods Page 7, line 162: Delete the words *"increase in risk in preeclampsia"*. There was no significant increased risk of preeclampsia found in current analysis.

We apologise for this error and have now corrected this statement in the revised manuscript.

Discussion Point #3: This point relates to limitations.

As noted above, the author's explanation for not adjusting for use of barrier contraception is not convincing because it appears the author has access to data on non-barrier contraception use among barrier contraception users. If so, a variable could be constructed to reflect the extent of barrier contraception use. Of concern, the Kho analysis of preeclampsia showed a much stronger association of duration of cohabitation with risk of preeclampsia and use of barrier contraception appears to be one of the only variables from the prior paper not considered in the current paper.

We have now corrected all results for use of barrier contraception.

Discrepant findings between Kho et al and current paper: *It is incumbent on the author to discuss possible reasons for why the preeclampsia findings in the present analysis are*

different from those published previously. It seems unlikely that the study population differed greatly between the time frames of the two analyses.

We have revised the discussion as requested. Pages 10-11, lines 253 – 263.

TITLE PAGE

The duration of sexual relationship and its effects on adverse pregnancy outcomes

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ABSTRACT

This study aims to determine if a short duration of sexual relationship is more common among women who experience adverse pregnancy outcomes including gestational hypertension (GHT), preeclampsia, small for gestational age (SGA) pregnancies and spontaneous preterm birth (sPTB) with or without abnormal uterine artery Doppler compared to women who have uncomplicated pregnancies. 5591 nulliparous women from the Screening for Pregnancy Endpoints (SCOPE) study were included. The risk for pregnancy complications for women who had a duration of sexual relationship of ≤3 months, 4-6 months, 7-9 months, 10-12 months was compared with women who had a duration of sexual relationship of > 12 months. Uterine artery Doppler was performed at 20 ± 1 weeks' gestation. A short duration of sexual relationship (≤ 3 months) was more common among women with SGA in the presence of abnormal uterine artery Doppler [9.8% vs 3.0%, aOR (95% CI) 3.4 (1.6-7.08] compared to women who had uncomplicated pregnancies. A short duration of sexual relationship (≤ 3 months) was also more common among women who had abnormal uterine artery Doppler compared to those with normal uterine artery Doppler [6.1% vs 3.1%, aOR (95% CI) = 2.1 (1.4-3.2)]. A short duration of sexual relationship was not associated with preeclampsia after adjusting for confounders. A short duration of sexual relationship is more common among women who deliver SGA infants with features of placental insufficiency as indicated by abnormal uterine artery Doppler.

Key words: duration of sexual relationship, preeclampsia, gestational hypertension, SGA, Uterine artery Doppler

INTRODUCTION

Prolonged exposure to paternal antigens in seminal fluid induces a state of maternal active immune tolerance to the fetus which facilitates successful placentation (Martinez-Varea et al., 2014). A maladaptive maternal immune response is proposed to result in impaired trophoblast invasion of spiral arteries, a characteristic feature of placental fetal growth restriction with or without the maternal preeclamptic syndrome (Redman et al., 1999, Huppertz, 2015). Repeated exposure to semen from the biological father of the baby over a prolonged time leads to development of maternal mucosal tolerance to these paternal antigens (Robertson et al., 2003, Robertson et al., 2002).

Martin and Herrmann in 1977 first reported that repeated exposure to semen from the biological father of the baby is associated with a reduced risk of preeclampsia (Marti and Herrmann, 1977). This was subsequently confirmed by other epidemiological studies which demonstrated that the duration of sexual cohabitation before conception was inversely related to the incidence of preeclampsia (Robillard et al., 1994, Einarsson et al., 2003, Saftlas et al., 2014) but refuted by another (Ness et al., 2004). We previously investigated the association between the duration of sexual relationship and its effects on gestational hypertension (GHT), preeclampsia and small for gestational age (SGA) pregnancies in a subset of the SCOPE (Screening fOr Pregnancy Endpoints study) cohort and found that a short duration of sexual relationship was more common among women who developed preeclampsia as well as among those women in the subgroup with SGA and abnormal uterine artery Doppler (Kho et al., 2009). In this study, we aim to investigate the above association in the entire SCOPE cohort and also that between a short duration of sexual relationship and other adverse pregnancy outcomes potentially associated with abnormal placentation namely spontaneous preterm birth (sPTB). Abnormal uterine artery Doppler waveform is a surrogate marker of impaired utero-placental perfusion.

Therefore, we also aimed to investigate the association between a short duration of sexual relationship and abnormal uterine artery Doppler at 20 ± 1 weeks' gestation.

MATERIALS AND METHODS

The participants of this study were women who were recruited to the SCOPE study between November 2004 and February 2011 in Adelaide, Australia, Auckland, New Zealand, Manchester, Leeds and London, United Kingdom and Cork, Ireland. The SCOPE study (www.scopestudy.net) is an international, multicentre, prospective cohort study with the aim of developing screening tests to predict preeclampsia, SGA infants and sPTB across different populations. Ethics approval was gained from local ethics committees of each participating centre (Australia REC 1712/5/2008, New Zealand AKX/02/00/364, Manchester, Leeds and London 06/MRE01/98, Cork ECM5 (10)05/02/08) and all women provided written informed consent.

A previous study by Kho and colleagues investigated the effects of a short duration of sexual relationship and preeclampsia and SGA pregnancies in the first 2507 women in the Adelaide and Auckland cohorts of the SCOPE study which included 2507 women. Here, we have included women from the entire SCOPE cohort of 5591. Recruitment of participants to the SCOPE study has previously been described in detail (Kho et al., 2009). In brief, participants were referred from hospital antenatal clinics, obstetricians, general practitioners, community midwives or self-referred. Nulliparous women with singleton pregnancies were recruited before 15 weeks' of gestation. Those considered at high risk of preeclampsia, SGA or preterm birth because of underlying medical conditions (including known pre-existing chronic hypertension on hypertensive medication or with a blood pressure >160/100 mmHg at 15 weeks of gestation), gynaecological history, three or more miscarriages or terminations of pregnancy or couples who received medical or surgical interventions which could modify

pregnancy outcome were not eligible. Participants were interviewed at 15 ± 1 and 20 ± 1 weeks' of gestation by SCOPE research midwives.

Recruited women were excluded from the present analyses if any of the following reasons applied: protocol violation, lost to follow up, multiple sexual partners and unsure of the identity of the biological father of the baby and miscarriage or termination (Figure 1). At the 15 ± 1 weeks' interview, data collected included demographic information, medical history, previous obstetric history, family history of obstetric complications and medical disorders. Current pregnancy data included information on any complications during current pregnancy, diet, smoking, alcohol and the use of recreational drugs. Details about the pre-pregnancy sexual history with the biological father of the index pregnancy including conception following the first episode of sexual intercourse and months of sexual relationship were obtained. The duration of sexual relationship was classified as conceived after a relationship of ≤ 3 months, ≤ 6 months and ≤ 12 months. Maternal physical measurements obtained at 15 ± 1 weeks of gestation included height, weight and blood pressure.

Uterine artery Doppler ultrasound was performed at 20 ± 1 weeks' gestation. Resistance indices (RI) for both uterine arteries were reported and the mean RI was calculated as the average of the two. If only a left or right uterine artery RI result was available, this was used as the mean RI. An abnormal uterine artery Doppler was defined as a mean resistance index > 90th percentile (Groom et al., 2009). All participants were followed prospectively and pregnancy outcome data and infant measurements were recorded by research midwives usually within 72 hours of birth.

Gestational hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation. *Preeclampsia* was defined as gestational hypertension or postpartum hypertension with proteinuria (24-h urinary protein 300 mg or spot urine protein : creatinine ratio ≥30 mg/mmol

creatinine or urine dipstick protein ≥++) or any multisystem complication of preeclampsia. Multisystem complications included any of acute renal insufficiency defined as a new increase in serum creatinine concentration ≥100 μmol/L antepartum or >130 μmol/L postpartum; effects on liver, defined as raised aspartate transaminase or alanine transaminase concentration, or both, >45 IU/L and/or severe right upper quadrant or epigastric pain or liver rupture; neurological effects included eclampsia, imminent eclampsia (severe headache with hyper-reflexia and persistent visual disturbance), or cerebral haemorrhage; and haematological effects included thrombocytopenia (platelets $<100\times10^9$/L), disseminated intravascular coagulation, or haemolysis (North et al., 2011). *Small for gestational age (SGA)* was defined as a birth weight below the 10th customised centile adjusted for maternal height, weight, parity and ethnicity, gestational age at delivery and infant sex (McCowan et al., 2004). *SGA with abnormal Doppler* was defined as birth of a SGA infant where the mother had a mean uterine artery RI >90th percentile at 20 ± 1 weeks' gestation. *Spontaneous preterm birth* (sPTB) was defined as spontaneous preterm labour or preterm premature rupture of membranes resulting in a preterm birth at <37 weeks. *Uncomplicated pregnancy* was defined as a pregnancy with no antenatal medical or obstetric complications and resulting in the delivery of an appropriately grown, healthy baby at ≥ 37 weeks' of gestation.

Statistical analyses were performed using R version 3.3.1 (cran.r-project.org). The data for each pregnancy complication (preeclampsia, preeclampsia with abnormal Doppler, gestational hypertension, SGA, SGA with abnormal Doppler and sPTB) was compared to the uncomplicated pregnancy group. For categorical variables, Chi-square test was used to compare the groups and for continuous variables, student's *t*-test or its non-parametric alternative was used as appropriate. Logistic regression was used to estimate odds ratios for each of the measures of variables of interest. For each variable, adjusted odds ratios were calculated by adding the following variables to the logistic regression model: maternal age,

ethnicity, primigravidity, BMI, mean arterial blood pressure, smoking status at 15 ± 1 weeks' gestation and use of barrier contraception. The independent variable was the duration of sexual relationship and the dependent variable was the pregnancy outcome. Complete data were available for all variables analysed. Results are reported as number and percent [n (%)] or mean ± standard deviation (SD) as appropriate. $P < 0.05$ was considered statistically significant. A retrospective power calculation was performed and demonstrated that we had >90% power to detect the observed increase in risk in SGA with abnormal Uterine artery Doppler and also in the comparison between normal and abnormal Uterine artery Doppler.

RESULTS

Of the 5690 pregnant women recruited, 5591 were eligible for this study (figure 1). Amongst these 5591, 3334 (59.6%) had uncomplicated pregnancies, 470 (8.4%) had gestational hypertension, 277 (4.9%) had preeclampsia, 628 (11.2%) had SGA infants, 234 (4.2%) had sPTB, 904 (16.2%) had other medical or obstetric complications including 173 (3.1%) with gestational diabetes mellitus (GDM). Of the 2257 women who had complicated pregnancies, 241 (10.7%) had more than one complication during pregnancy (figure1).

The characteristics of the participants according to pregnancy outcome are shown in table 1. A short duration of sexual relationship (≤3 months and 4-6 months) was more common among women who developed preeclampsia compared to those with uncomplicated pregnancies (≤ 3 months, 4.7% vs 3.0% and 4-66 months 6.5% vs 3.8%, table 2) but after adjusting for confounders a short duration of sexual relationship was not significantly associated with preeclampsia (table 2). A short duration of sexual relationship was also not significantly associated with preeclampsia in the group of women who had abnormal uterine artery Doppler at 20 ± 1 weeks' (table2). A short duration of sexual relationship (≤3 months and 4-6 months) was more common among women who had SGA infants compared to those with uncomplicated

pregnancies (≤ 3 months, 4.7% vs 3.0% and 4-6 months 5.4% vs 3.8%, table 3) but after adjusting for confounders a short duration of sexual relationship was not significantly associated with SGA (table 3). A short duration of sexual relationship was more common among women who had SGA infants and also had an abnormal uterine artery Doppler at 20 ± 1 weeks' compared to those who had uncomplicated pregnancies (9.8% vs 3% for ≤ 3 months and 5.4% vs 3.8% for 4-6 months; table 3). After adjusting for confounders, compared to women who had uncomplicated pregnancies, women who had SGA infants plus an abnormal uterine artery Doppler were 3.4 times as likely to have a sexual relationship of ≤ 3 months (table 3). The duration of sexual relationship was not associated with gestational hypertension (supplementary table 1) or spontaneous preterm birth (supplementary table 2). A short duration of sexual relationship was more common among women who had abnormal uterine artery Doppler at 20 ± 1 weeks' compared to women who had normal uterine artery Doppler studies (6.1% vs 3.0 % for ≤ 3 months and 5.0% vs 4.3% for 4-6 months; table 4). After adjusting for confounding factors, compared to women who had normal Uterine artery Doppler, women who had abnormal Uterine artery Doppler were 2.1 times as likely to have a sexual relationship of ≤ 3 months (table 4).

DISCUSSION

This large prospective cohort study of 5591 women demonstrates that a short duration of sexual relationship associates with a pregnancy complicated by SGA in the presence of abnormal uterine artery Doppler indices at 20 ± 1 weeks'. Our study also shows that abnormal uterine artery Doppler RI at 20 ± 1 weeks' is more common among women who have a short duration of sexual relationship.

In our previous study, we demonstrated for the first time that a short duration of sexual relationship (≤ 6 months) was associated with increased risk for SGA (Kho et al., 2009).

Although this association was evident on univariate analysis, the effect was not significant after adjusting for potential confounding factors (Kho et al., 2009). We found similar results for our analyses on the groups of women with a duration of sexual relationship ≤ 3 months and 4-6 months. In addition, in the previous study, the association between short duration of sexual relationship and SGA with abnormal uterine artery Doppler was identified for the first time (Kho et al., 2009). We demonstrated a 2.8 fold increase in short duration of sexual relationship in this subgroup of SGA pregnancies (Kho et al., 2009). In our present study, we have confirmed our previous findings in a larger cohort and have demonstrated that a short duration of sexual relationship (≤ 3 months) increases the risk for SGA with abnormal uterine artery Doppler. Successful placentation requires a cascade of reactions of the innate and adaptive immune systems, which critically regulate the invasion of fetal placental derived extravillous cytotrophoblasts into the maternal decidua and spiral arteries (Khong et al., 1986). Seminal fluid TGFβ is proposed to inhibit the induction of type 1 immune responses against the semi-allogenic conceptus that are thought to be associated with impaired placentation and spiral artery remodelling which are features of preeclampsia and intrauterine growth restriction (Khong et al., 1986, Leonard et al., 2006, Robertson et al., 2002). In our present study, we also assessed the relationship between a short duration of sexual relationship and abnormal uterine artery Doppler studies. We found that a short duration of sexual relationship (≤ 3 months) increases the risk of abnormal uterine artery Doppler at 20 ± 1 weeks' suggesting a possible mechanistic pathway for the association between a short duration of sexual relationship and the SGA subgroup with abnormal uterine artery Doppler.

In our present study, a short duration of sexual relationship was not associated with preeclampsia after adjusting for confounding factors. Previous studies on the relationship between a short duration of sexual relationship and preeclampsia have reported mixed results. Our previous findings from the Adelaide and Auckland cohort of the SCOPE study which

included 2507 women (Kho et al., 2009) and studies from France (n = 1011), Spain (n =339) and USA (n = 440) all demonstrated an inverse association between the duration of sexual relationship and the risk of preeclampsia (Robillard et al., 1994, Einarsson et al., 2003). However, a previous prospective study of 2211 women of mixed parity from USA reported that "time to conception" was not associated with the risk of preeclampsia (Ness et al., 2004). The difference between the study by Ness et al and the others could be due to the inclusion of multiparous women in the study by Ness et al. Multiparous women are less likely to develop preeclampsia than nulliparous women, and the possibility of change in partners between pregnancies and the inter-pregnancy interval that influence subsequent pregnancies was not addressed in the Ness et al study (Lie et al., 1998, Skjaerven et al., 2002). The protective effect of a lengthy sexual relationship on preeclampsia has been partly explained by the theory of "maternal mucosal tolerance to paternal antigens" (Robertson et al., 2003). Deposition of semen in the female genital tract induces a cascade of events that result in a classic inflammatory response. Transforming growth factor beta (TGFβ), a cytokine present in abundance in seminal plasma, initiates this inflammatory response by stimulating the synthesis of pro-inflammatory cytokines and chemokines in uterine tissues (Robertson et al., 2003). TGFβ elicits strong type 2 and Th3 immune responses towards antigens present in semen (Robertson et al., 2002). Repeated sexual intercourse with sustained antigen exposure in an environment mediated by TGFβ is proposed to be essential in the partner-specific mucosal tolerance (Robertson et al., 2002). The different results observed in the many studies could be due to the different phenotypes of preeclampsia. The difference between our previous findings on a subset of SCOPE women and our current findings on the entire SCOPE cohort may be due to the inclusion of a larger number of women with "maternal preeclampsia" phenotype in the current study. This type of preeclampsia, first proposed by Redman and Sargent (Redman and Sargent, 2003) is a phenotype of preeclampsia that is not linked to impaired spiral artery

remodelling. These women were also diagnosed at term (>37 weeks' gestation) or late preterm (34-37 weeks' gestation. Our group of preeclamptic women who also had abnormal uterine artery Doppler also had a shorter duration of sexual relationship but insufficient power may explain the lack of statistical significance. The fact that the majority of preeclamptic women did not have an abnormal uterine artery Doppler also demonstrates that the majority of women in our cohort had the "maternal preeclampsia, i.e. the phenotype of preeclampsia not associated with reduced remodelling of the spiral arteries by invading cytotrophoblast.

We did not see a significant association between a short duration of sexual relationship and either gestational hypertension or spontaneous preterm birth. Although our large prospective cohort study demonstrates that a short duration of sexual relationship is a risk for SGA pregnancies and the SGA subgroup with abnormal uterine artery Doppler, our study has inherent limitations that are unavoidable in studies that investigate semen exposure in the pre-conceptional period. It was not feasible to collect information prospectively on semen exposure as many pregnancies are unplanned. The data collected on the length of sexual relationship is potentially subject to recall bias.

CONCLUSION

This large prospective study demonstrates that a short duration of sexual relationship is more common among women who deliver SGA infants with features of placental insufficiency as indicated by abnormal uterine artery Doppler.

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Disclosure statement: The authors report no conflict of interest

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Table 1 Maternal characteristics

	Uncomplicated (N = 3334)	Preeclampsia (N = 277)	P value	GH (N = 470)	P value	SGA (N = 628)	P value	sPTB (N = 234)	P value
Age (years)	28.81 ± 5.35	27.68 ± 5.72	0.001	28.81 ± 5.39	0.96	28.61 ± 5.76	0.53	28.24 ± 5.9	0.24
Ethnicity			0.44		0.002		0.13		0.39
European	3020 (90.58%)	246 (88.81%)		441 (93.83%)		559 (89.01%)		212 (90.6%)	
Polynesian	69 (2.07%)	9 (3.25%)		11 (2.34%)		13 (2.07%)		3 (1.28%)	
Asian	109 (3.27%)	7 (2.53%)		2 (0.43%)		16 (2.55%)		5 (2.14%)	
Indian	63 (1.89%)	7 (2.53%)		8 (1.7%)		19 (3.03%)		8 (3.42%)	
Other	73 (2.19%)	8 (2.89%)		8 (1.7%)		21 (3.34%)		6 (2.56%)	
Gravidity			0.77		0.054		0.0421		0.0004
1	2600 (77.98%)	212 (76.53%)		385 (81.91%)		462 (73.57%)		159 (67.95%)	
2	570 (17.1%)	52 (18.77%)		72 (15.32%)		133 (21.18%)		51 (21.79%)	
≥ 3	164 (4.92%)	13 (4.69%)		13 (2.77%)		33 (5.25%)		24 (10.26%)	
At 15 ± 1 weeks									
Smoking	305 (9.15%)	27 (9.75%)	0.75	45 (9.57%)	0.73	118 (18.79%)	<0.0001	41 (17.52%)	0.0001
Body mass index (kg/m2)	24.77 ± 4.33	27.76 ± 6.28	<0.0001	27.91 ± 5.79	<0.0001	25.9 ± 5.47	<0.0001	25.45 ± 5.41	0.23
SBP (mmHg)	105 ± 10	112 ± 11	<0.0001	114 ± 10	<0.0001	108 ± 11	<0.0001	107 ± 11	0.0115
DBP (mmHg)	64.18 ± 7.4	69.11 ± 8.13	<0.0001	71 ± 8	<0.0001	66 ± 8	<0.0001	65 ± 8	0.0287
Pregnancy outcome									
Gestation at delivery (weeks)	40.17 ± 1.16	38.03 ± 2.72	<0.0001	39.6 ± 1.95	<0.0001	38.83 ± 3.52	<0.0001	33.81 ± 3.92	<0.0001
Birthweight (g)	3591 ± 397	3028 ± 802	<0.0001	3331 ± 594	<0.0001	2607 ± 579	<0.0001	2358 ± 740	<0.0001
Birthweight centile	54 ± 25	40 ± 32	<0.0001	40 ± 30	<0.0001	5 ± 3	<0.0001	49 ± 31	0.017

Results are expressed as mean ± SD or N (%). All p values are for comparison of complicated pregnancy group with uncomplicated. SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 2 Duration of sexual relationship and preeclampsia and preeclampsia with abnormal Uterine artery Doppler

Months of sexual relationship	Uncomplicated (N = 3354)	PE (N = 277)	aOR (95% CI)	PE with abnormal Doppler (N = 52)	aOR (95% CI)
0 - 3	101 (3.03)	13 (4.69)	1.08 (0.56-2.06)	4 (7.69)	2.87 (0.92-8.94)
4 - 6	126 (3.78)	18 (6.50)	1.33 (0.76-2.33)	3 (5.77)	1.32 (0.37-4.66)
7 - 9	115 (3.45)	10 (3.61)	0.75 (0.37-1.53)	4 (7.69)	1.79 (0.56-5.65)
10 - 12	128 (3.84)	8 (2.89)	0.62 (0.29-1.32)	3 (5.77)	1.39 (0.4-4.78)
> 12	2864 (85.90)	228 (82.31)	ref	38 (73.08)	ref

PE, preeclampsia, results are expressed as N (%).
Adjusted OR (95% CI) are adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status at 15 weeks' gestation and use of barrier contraception

Table 3 Duration of sexual relationship and SGA and SGA with abnormal Uterine artery Doppler

Months of sexual relationship	Uncomplicated (N = 3354)	SGA (N = 628)	aOR (95% CI)	SGA with abnormal Doppler (N = 112)	aOR (95% CI)
0 - 3	101 (3.03)	29 (4.62)	1.3 (0.83-2.04)	11 (9.82)	3.4 (1.64-7.08)
4 - 6	126 (3.78)	34 (5.41)	1.33 (0.88-2)	6 (5.36)	1.57 (0.64-3.82)
7 - 9	115 (3.45)	22 (3.50)	0.91 (0.56-1.49)	6 (5.36)	1.75 (0.71-4.32)
10 - 12	128 (3.84)	33 (5.25)	1.26 (0.84-1.9)	8 (7.14)	2.15 (0.99-4.65)
> 12	2864 (85.90)	510 (81.21)	ref	81 (72.32)	ref

SGA, small for gestational age, results are expressed as N (%).
Adjusted OR (95% CI) are adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status at 15 weeks' gestation and use of barrier contraception

Table 4 Duration of sexual relationship and uterine artery Doppler

Months of sexual relationship	Normal Uterine artery Doppler (N = 4825)	Abnormal Uterine artery Doppler (N = 524)	aOR (95% CI)
0 - 3	149 (3.09)	32 (6.11)	2.11 (1.39-3.21)
4 - 6	211 (4.37)	26 (4.96)	1.21 (0.78-1.88)
7 - 9	166 (3.44)	25 (4.77)	1.47 (0.94-2.3)
10 - 12	203 (4.21)	25 (4.77)	1.22 (0.78-1.88)
> 12	4096 (84.89)	416 (79.39)	ref

Results are expressed as N (%).
Adjusted OR (95% CI) are adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status at 15 weeks' gestation and use of barrier contraception

Figure legends

Figure 1 Study Population

[*] Includes 70 preeclampsia (PE) and small for gestational age (SGA). [**] Includes 96 gestational hypertension and SGA. [#] Includes 26 spontaneous preterm birth (SPTB) and SGA, 7 SPTB and preeclampsia. [^] Includes 19 gestational diabetes (GDM) and PE, 14 GDM and SPTB, 11 GDM and SGA, 16 GDM and GH. [$] Admission to hospital for other significant medical or surgical conditions, antepartum haemorrhage, chromosomal abnormalities and congenital anomalies.

Figure 2 Duration of sexual relationship and pregnancy outcome

OR (95% CI) are for predicted probability of pregnancy complications for every 12 months increase in the duration of sexual relationship

Figure 3 Duration of sexual relationship and abnormal Uterine artery Doppler

OR (95% CI) are for predicted probability of abnormal Uterine artery Doppler for every 12 months increase in the duration of sexual relationship

- A short sexual relationship is common in women who have abnormal uterine artery Doppler
- It is also common in the above group who also deliver SGA infants
- A short sexual relationship appears to be more common in women who have placental insufficiency

Supplementary table 1 Duration of sexual relationship and gestational hypertension

Months of sexual relationship	Uncomplicated (N = 3354)	GHT (N = 470)	aOR (95% CI)
0 - 3	101 (3.03)	12 (2.55%)	0.73 (0.37-1.41)
4 - 6	126 (3.78)	26 (5.53%)	1.39 (0.85-2.27)
7 - 9	115 (3.45)	12 (2.55%)	0.68 (0.36-1.32)
10 - 12	128 (3.84)	21 (4.47%)	1.08 (0.64-1.8)
> 12	2864 (85.90)	399 (84.89%)	ref

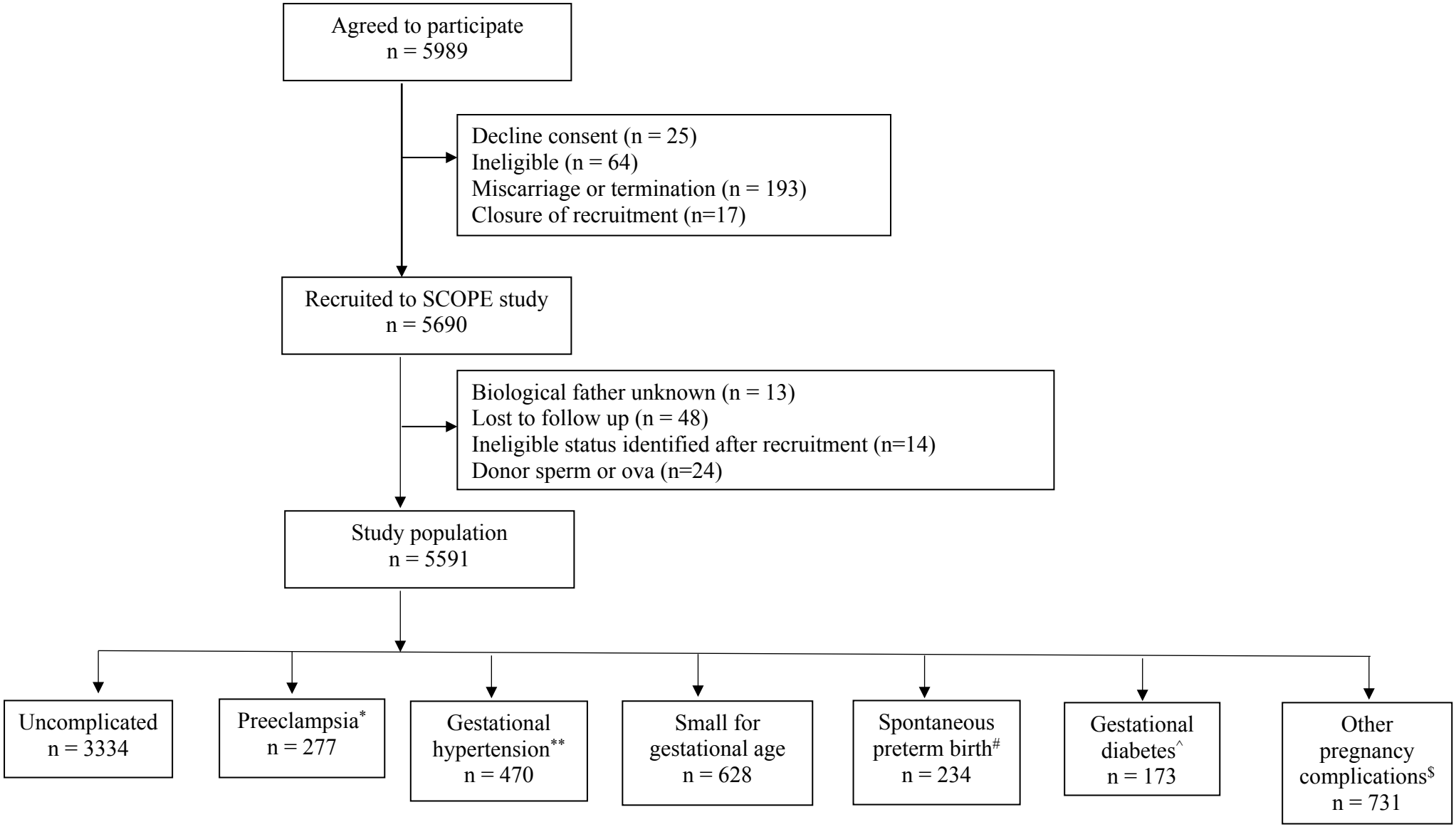
GHT, gestational hypertension, results are expressed as N (%).
Adjusted OR (95% CI) are adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status at 15 weeks' gestation and use of barrier contraception

Supplementary table 2 Duration of sexual relationship and spontaneous preterm birth

Months of sexual relationship	Uncomplicated (N = 3354)	sPTB (N = 234)	aOR (95% CI)
0 - 3	101 (3.03)	10 (4.27)	1.07 (0.53-2.16)
4 - 6	126 (3.78)	8 (3.42)	0.74 (0.35-1.57)
7 - 9	115 (3.45)	11 (4.70)	1.11 (0.57-2.17)
10 - 12	128 (3.84)	10 (4.27)	0.9 (0.46-1.78)
> 12	2864 (85.90)	195 (83.33)	ref

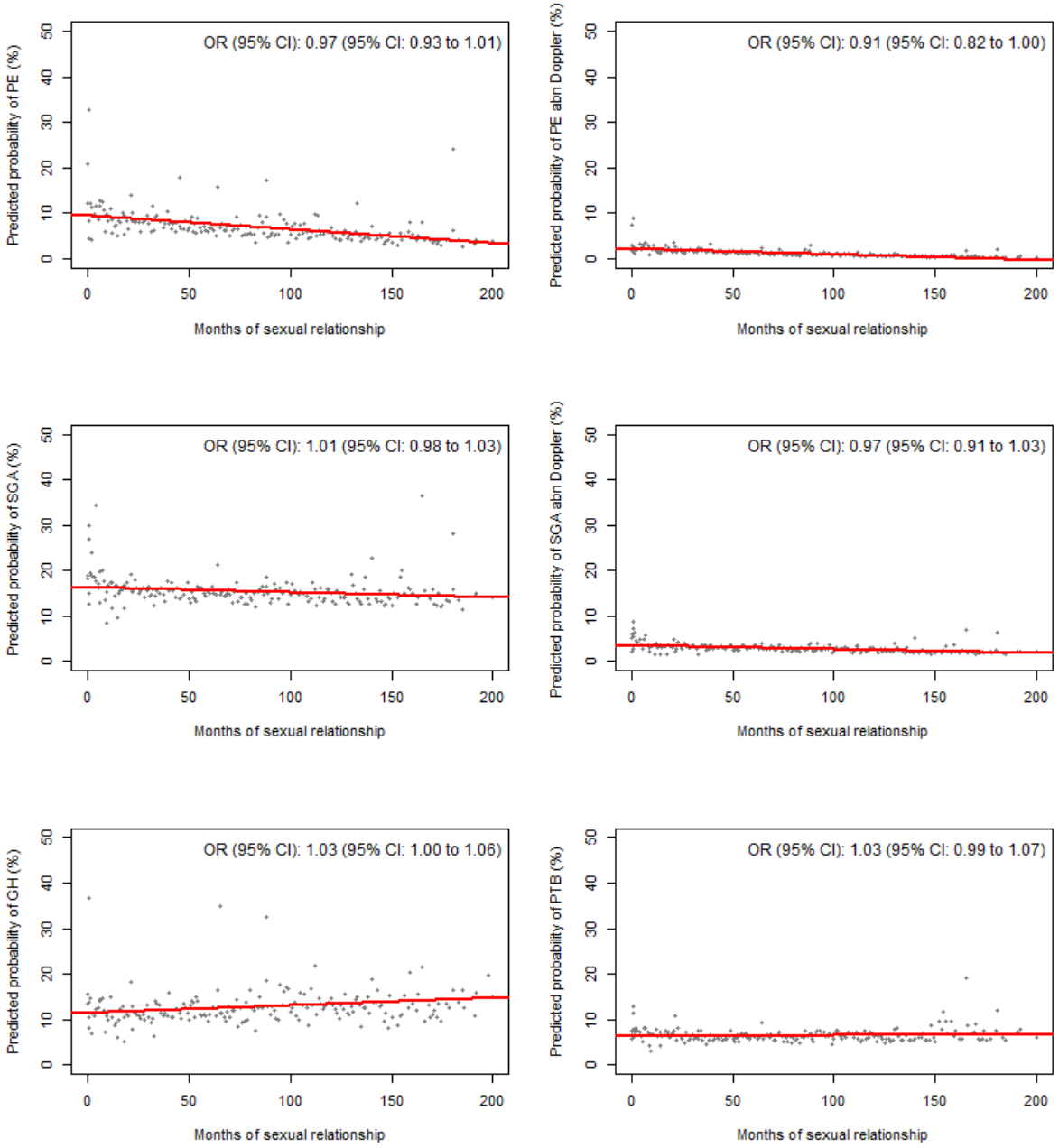
sPTB, spontaneous preterm birth, results are expressed as N (%).
Adjusted OR (95% CI) are adjusted for age, ethnicity, BMI, primigravidity, mean arterial blood pressure and smoking status at 15 weeks' gestation and use of barrier contraception

Figure 1 Study Population



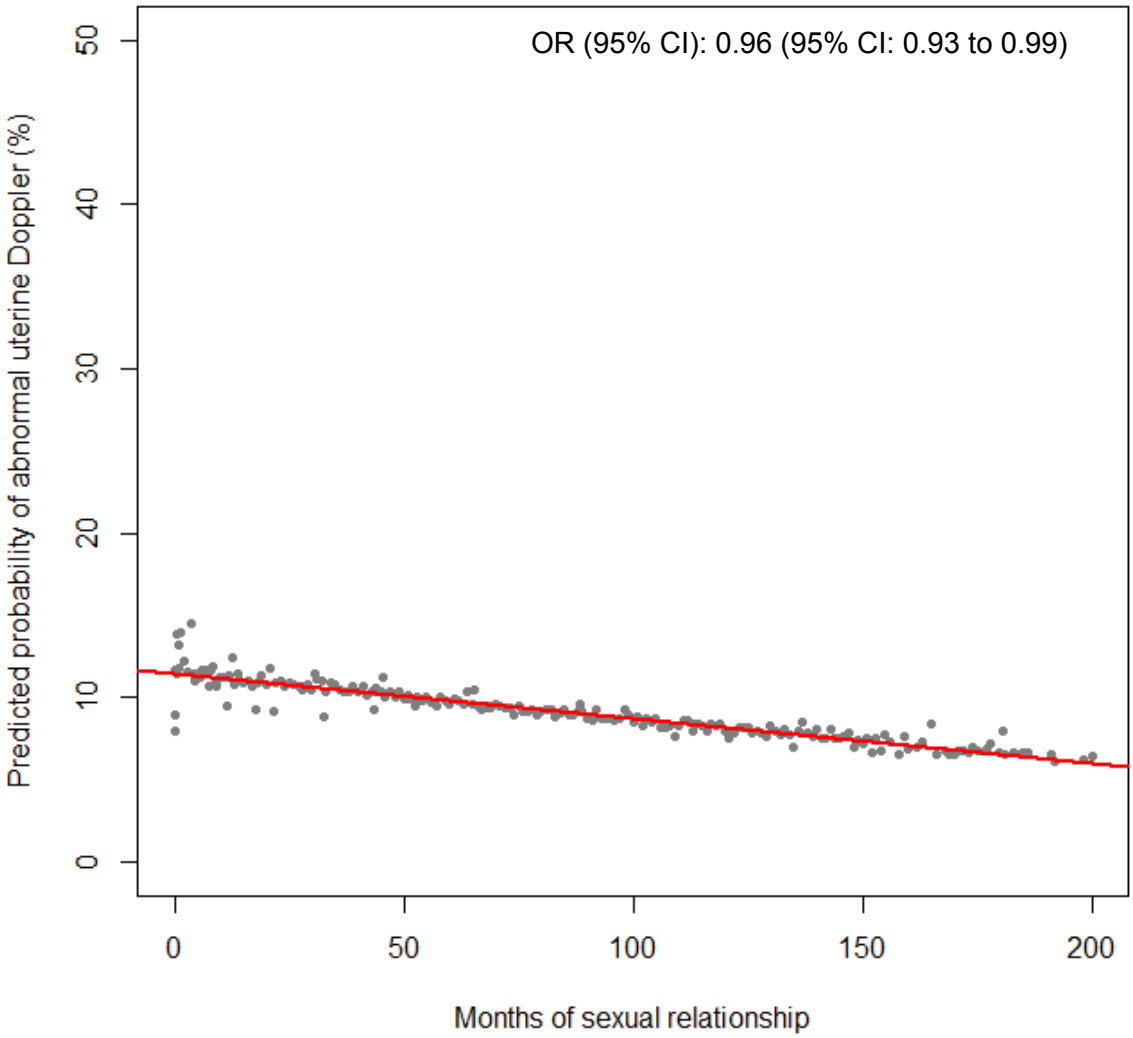
[*] Includes 70 preeclampsia (PE) and small for gestational age (SGA). [**] Includes 96 gestational hypertension and SGA. [#] Includes 26 spontaneous preterm birth (SPTB) and SGA, 7 SPTB and preeclampsia. [^] Includes 19 gestational diabetes (GDM) and PE, 14 GDM and SPTB, 11 GDM and SGA, 16 GDM and GH. [$] Admission to hospital for other significant medical or surgical conditions, antepartum haemorrhage, chromosomal abnormalities and congenital anomalies.

Figure 2 Duration of sexual relationship and pregnancy outcome



OR (95% CI) are for predicted probability of pregnancy complications for every 12 months increase in the duration of sexual relationship

Figure 3 Duration of sexual relationship and abnormal Uterine artery Doppler



OR (95% CI) are for predicted probability of abnormal Uterine artery Doppler for every 12 months increase in the duration of sexual relationship

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