Influence of adenomyosis on pregnancy and perinatal outcomes in women with endometriosis

Short Title: Adenomyosis and pregnancy outcome

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Abstract

OBJECTIVES: Several studies investigated the correlation between endometriosis and adverse pregnancy and perinatal outcomes. However, the role of adenomyosis as a risk factor for adverse perinatal outcomes in women with endometriosis has yet to be established. The aim of this study

was to explore if fetal and maternal outcomes, in particular the incidence of small for gestational age (SGA) infants, are different in pregnant women with endometriosis (E) and the concomitant presence of diffuse (EDA) and focal ademonyosis (EFA).

METHODS: This is a retrospective analysis of a database collected prospectively during a three-year period. We included 206 pregnant women with endometriosis; 148 (71.8%) with E, 38 (18.4%) with EFA and 20 (9.7%) with EDA. Adenomyosis was diagnosed by ultrasonography, it was classified in focal or diffuse. The study included patients who conceived spontaneously or by assisted reproductive techniques.

RESULTS: The three groups were similar in demographic characteristics (age, body mass index, mode of conception). Patients with diffuse adenomyosis compared with those with only endometriosis had significantly lower PAPP-A MoM (0.61 vs 0.88 MoM, $p<0.001$), higher mean uterine artery pulsatility index (UtA PI) in the 1st (2.23 vs 1.67, $p<0.001$) and 2nd (1.30 vs 0.94, $p<0.001$) trimester of pregnancy, and higher incidence of SGA (40% vs 10.8%, $p<0.001$; respectively). No statistically significant difference was found in patients with focal adenomyosis compared to those with only endometriosis. Logistic regression analysis demonstrated that diffuse adenomyosis (OR=3.744 CI 95%1.158-12.099; $p=0.027$) was the only independent risk factors for SGA.

CONCLUSIONS: The presence of diffuse adenomyosis in pregnant women with endometriosis is is strongly associated with SGA infants. Women with diffuse adenomyosis should be treated as being at high risk of placental dysfunction, therefore, these pregnancies might need a closer monitoring.

Introduction

Endometriosis and adenomyosis are defined by the presence of endometrial glands and stroma, located outside the uterus and in the myometrial wall, respectively [1]. The eutopic endometrium, as well as the inner myometrium, in patients affected by endometriosis and/or adenomyosis, shows several functional and structural abnormalities [1]. These differences seem to be mainly related to an abnormal expression of genes involved in local estrogen production and response to progesterone, an altered oxidative stress response, presence of cytokines, inflammatory mediators, and apoptotic markers [2, 3].

In the last ten years, several studies reported a correlation between endometriosis and major obstetrical adverse outcomes, such as spontaneous late miscarriage [4], preterm premature rupture of the membranes and preterm birth [5-11], small for gestational age (SGA) [5, 10], hypertension [9], pre-eclampsia [5, 8, 11], gestational diabetes [10], obstetric hemorrhages (such as abruptio placentae and postpartum bleeding) [5, 9, 11] and placenta previa [5-7, 9, 12]. However, other studies [12, 13] and a systematic review [14] did not completely confirm the increased risk of obstetrical complications in women with endometriosis. Theoretically, some pathogenic mechanisms might explain the higher risk of obstetrical complications in women with endometriosis; these mechanisms include endometrial resistance to selective actions of progesterone, inflammation, inadequate uterine contractility, endometrial excessive activation of free radical metabolism and the presence of an abnormal throphoblastic invasion into the ‘‘myometrial junctional zone’’ (JZ) due to the partial or absent remodelling of the myometrial spiral arteries [15].

It is well known that there is a high association between endometriosis and adenomyosis [16]. The reported prevalence of adenomyosis in patients affected by endometriosis range widely between 20% to 50% [17-19] and its association seems to be related with increasing age, parity, dysmenorrhea intensity and with the presence of deep infiltrating endometriosis (DIE) [20]. Previous studies also showed that women with adenomyosis are at increased risk of some adverse pregnancy outcomes (such as preterm delivery, preterm premature rupture of membrane, SGA infants and fetal

malpresentation) [21-23]. However, despite this background, previous studies gave little attention to the influence of adenomyosis on the pregnancy outcomes of patients with endometriosis.

On the basis of these premises, the aim of the present study was to evaluate the maternal and fetal outcomes in a cohort of women with endometriosis with or without the concomitant presence of diffuse or focal adenomyosis.

Methods

Study design and study population

This study was based on a retrospective analysis of a database collected prospectively between January 2014 and December 2016. The study protocol was approved by the Regional Ethic Committee. Patients included in the study signed a general consent form for the use of their data for scientific purposes.

This study included pregnant women who had ultrasonographic and/or histological diagnosis of endometriosis and ultrasonographic diagnosis of focal or diffuse adenomyosis prior to conception. The ultrasonographic exams were performed at any phase of the menstrual cycle regardless of the use of hormonal therapy. Standardized ultrasound criteria were used for the diagnosis of DIE [24] and endometriomas [25]. The ultrasonographic diagnosis of adenomyosis was made if two of more of the following features were present: asymmetrical myometrial thickening, myometrial cysts, linear striations, hyperechoic islands, or an irregular and thickened endometrial-myometrial junction zone on either two-dimensional or three-dimensional imaging [26, 27]. At ultrasonography, focal adenomyosis was defined as the presence of adenomyosis-related lesions in only one part of the myometrium; while diffuse adenomyosis was defined as the presence of ill-defined lesions in more than one site within the uterine wall, more often being dispersed within the myometrium rather than forming a confined lesion [28].

The patients included in the study were divided into three groups: patients with endometriosis and focal adenomyosis (EFA), patients with endometriosis and diffuse adenomyosis (EDA) and patients with only endometriosis (E).

Women with previous uterine surgery or uterine malformations, pregnancies with major fetal structural abnormalities, with chronic hypertension disease, with known autoimmune diseases, fetal aneuploidy or multiple gestations were excluded.

Pregnancies were dated by measurements of crown-rump length (CRL) in the first trimester according to the National Institute for Health and Clinical Excellence (NICE) guidelines [29]. PAPP-A levels were measured at the time of routine 11-14 weeks' first-trimester combined screening test for Down syndrome. Uterine artery (UtA) Doppler indices were measured at the time of routine 11-14 weeks' and at the time of routine anomaly scan between 19-23 weeks of gestation in all of the women. UtA Doppler assessment was performed transabdominally [30]. Pulsatility index (PI) of the left and the right UtA was averaged to compute mean PI and plotted against a published reference range [30]. All the patients underwent a growth scan during the 3rd trimester of pregnancy between 29-34 weeks of gestation to evaluate the growth of the fetus. Low-dose aspirin for prevention of preeclampsia was not used during the study period. Ultrasound assessments were performed using GE Voluson E6 (GE Healthcare, Zipf, Austria). Maternal characteristics, including age, body mass index (BMI), ethnic origin, and the type of conception, spontaneous or in vitro fertilization (IVF), were recorded during the first visit and the outcomes of pregnancies were collected. Delivery or follow-up scans were arranged as appropriate for any suboptimal assessments.

Gestational complications were defined as follows: preterm birth was a delivery before 37 completed weeks of gestation; pregnancy induced hypertension (PIH) was blood pressure persistently over 140/90 mm Hg developed after 20 weeks of gestation in a previously normotensive woman; preeclampsia was gestational hypertension and proteinuria (>300 mg/24 hours); SGA indicated an infant with birth weight less than the 10th centile for gestational age.

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 x^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 [29]. UtA mean PI was corrected for gestational age and multiple of medians were calculated on the reference ranges from the published centiles [29]. Logistic regression analysis was used to assess the association of maternal characteristics, first- and second-trimester markers, and fetal outcomes for women with endometriosis and diffuse and focal adenomyosis and SGA; $P < .05$ was considered statistically significant. Statistical analysis was performed using statistical software (SPSS 20.0; SPSS Inc, Chicago, IL).

Results

The demographic and pregnancy characteristics of the three groups of patients are presented in Table 1 and Table 2.

During the study period 206 pregnant women with endometriosis were recruited in the study and had the complete follow-up required for the study. Among these patients, 148 (71.8%) had E, 38 (18.4%) had EFA and 20 (9.7%) had EDA.

Compared to women with E, those presenting with EDA had statistically significant lower BMI, lower first trimester PAPP-A levels, had significantly higher first trimester and mid-pregnancy mean UtA Doppler PI. The prevalence of SGA fetuses calculated from the ultrasound estimated fetal weight (EFW) centile during the 3rd trimester scan assessment was significantly different for women with only endometriosis (10.8%) versus women with EDA (30%, $P < .05$). These results were confirmed after delivery, since the prevalence of SGA birth in women presenting with only endometriosis versus the women with EDA was 10.8% (16) and 40% (8) respectively ($P < .05$). No

statistically significant difference was found on the 5 minute Apgar score and in the prevalence of preeclampsia between the two cohorts of patients (Table 1).

Compared to women with E, those presenting with EFA had no statistically significant difference regarding maternal demographics, no statistically significant difference in the first trimester PAPP-A levels, first trimester and mid-pregnancy mean UtA Doppler PI, estimated fetal weight (EFW) centile and SGA fetuses prevalence. Moreover, no statistically significant difference was found in the SGA birth prevalence, 5 minute Apgar score and in the prevalence of preeclampsia between the two groups (Table 2).

Logistic regression analysis was used to assess the relation between maternal and pregnancy characteristics with SGA and EDA and EFA; the results are presented in Table 3 and Table 4. The presence of EDA was the only parameter independently associated with the delivery of SGA infants.

Discussion

Main Findings

The study demonstrates that the presence of diffuse adenomyosis in pregnant women with endometriosis are associated with an increased risk of delivery a SGA infant. When assessed in isolation, conventional risk factors for placental insufficiency such as BMI, PAPP-A and mean UtA Doppler PI during the first and the second trimester of pregnancy showed a strong correlation with the presence of diffuse adenomyosis in patients with endometriosis. At the time of the 3rd trimester scan assessment, the prevalence of SGA fetuses was significantly higher in the cohort of patients with EDA compared to those with only endometriosis, and these data were confirmed after delivery. After adjusting the results for potential confounding variables, such as BMI and PAPP-A, logistic regression analysis demonstrated that only the presence of EDA was associated with the occurrence of SGA at birth, while the presence of EFA was not associated with the delivery of an SGA infant.

The study results strongly suggest that the presence of EDA increased the risk of having an infant with SGA and they support a potential causative relation between EDA and impaired placentation and subsequent development of SGA.

Interpretation

In the last ten years, research has been focused on the influence of endometriosis on pregnancy outcomes [4-13, 31-34]. The data reported in the current literature are controversial and a systematic review concluded that there is no evidence that endometriosis has a major detrimental effect on pregnancy outcome [14]. However, this review found a correlation of endometriosis with placenta previa with odds ratio raging from 1.67 to 15.1 [14]. In a recent retrospective case-control study including women achieving singleton pregnancy by IVF, Benaglia *et al.* found that women with endometriosis do not have an increased risk of preterm birth, hypertensive disorders, gestational diabetes, small and large for gestational age newborns and neonatal problems. In contrast, the

authors confirmed that placenta previa was more common in women with endometriosis than in controls [12]. Surprisingly, most of the published studies did not assess the impact of adenomyosis on pregnancy outcome of patients with endometriosis. This was due to the fact that in most of the studies the data were retrospectively collected and analyzed [7, 12, 13, 31, 33], or they were based on computerized national [4-6, 8, 11] or institutional [32] databases, or the data were collected only at the time of delivery [10, 34]; therefore, a preconceptional ultrasonographic assessment of adenomyosis was not performed. Very recently, a cohort study found no significant difference in the incidence of complications during pregnancy and delivery of patients with rectovaginal DIE with and without an ultrasound diagnosis of adenomyosis [9]. However, in this study the small sample size may have limited the strength of the analysis, in fact only 30 patients with posterior DIE and adenomyosis were compared with 22 patients with posterior DIE without adenomyosis; furthermore, no subanalysis according to the type of adenomyosis was performed [9].

Our study investigated, for the first time in literature, the influence of diffuse and focal adenomyosis in a cohort of patients with endometriosis on the adverse pregnancy outcomes, revealing that the concomitant presence of diffuse adenomyosis in pregnant women with endometriosis is an important risk factor of placental insufficiency a consequent delivery of SGA infants.

The presence of adenomyosis seems to affect the process of the junctional zone (JZ) spiral artery remodelling from the onset of decidualization and result in vascular resistance and increased risk of defective deep placentation [35]. Yorifuji *et al.* measured the blood flow in the myometrium and placenta using time-slip magnetic resonance angiography in women with adenomyosis who had severe fetal growth restriction and they found that the uterine adenomyosis area showed abundant blood flow while the placenta had diminished blood flow, suggesting un unbalanced perfusion of the placenta to be among the possible causes of SGA [36]. Furthermore, a case-control study based on a cohort population of 2138 pregnant women found that pregnant women with adenomyosis have higher rates of preterm delivery and preterm premature rupture of the membranes (pPROM),

probably due the increased local inflammatory response and the higher levels of prostaglandins found in these patients [22]. More recently, a Japanese retrospective study based on the review of a computerized database compared pregnancy outcomes of 36 women diagnosed with adenomyosis before conception to 144 control women without uterine abnormalities [23]. The authors found that women with adenomyosis have higher risk of preterm delivery, preterm premature rupture of membrane, SGA infants, fetal malpresentation and cesarean delivery [23]. In agreement with these findings, another Japanese retrospective case-control study including 49 singleton pregnancy complicated by adenomyosis and 245 controls showed that patients with adenomyosis have increased risk of second trimester miscarriage, preeclampsia, placental malposition and preterm delivery [21].

Strength and limitation

This study has some limitations. First, this is a retrospective study, although the data were collected prospectively. Second, the sample size was relatively small, especially in subgroups analysis. The small number of pregnant women with endometriosis and adenomyosis did not allow performing a further subanalysis according to the form of endometriosis diagnosed by ultrasonography (i.e. ovarian endometriomas or DIE). However, these preliminary findings may pave the way for future studies with larger sample size. Finally, we did not exclude patient who conceived by IVF procedures, and this could be a potential bias on the prevalence of adverse pregnancy outcome, such as preeclampsia, even though the number of IVF conceptions were quite small and they were similar between the study groups. The main strength of this study is that we study separately the subgroups of women with EDA and EFA compared to those with only endometriosis, leading to a clear understanding of the role of the different forms of adenomyosis in the pregnancy adverse outcomes.

Conclusions

In conclusion, the current study shows that diffuse adenomyosis in pregnant women with endometriosis is strongly associated with SGA infants. Women with endometriosis and diffuse adenomyosis should be treated as being at high risk of placental dysfunction and might need a closer monitoring during pregnancy. These results are also potentially useful for preconception and prenatal counseling of women with both adenomyosis and endometriosis.

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Tables

Table 1. Comparison between pregnant women with EDA and women with only endometriosis

	Total (n = 168)	**EDA** (n = 20)	**Only Endometriosis** (n = 148)	**P value**
Demographics				
Maternal age, (years, median, IQR)	30.0 (27.0-33.0)	31.0 (27.0-33.0)	30.0 (27.0-33.0)	0.522
Nulliparous (n, %)	141 (83.9)	18 (90.0)	123 (83.1)	0.431
BMI (kg/m^2, median, IQR)	23.3 (20.6-26.5)	21.2 (19.5-24.2)	23.7 (20.9-26.5)	0.043
Race (n, %) • Caucasian • Afro-Caribbean • Asian	 142 (84.5) 18 (10.7) 8 (4.7)	 17 (85.0) 2 (10) 1 (5.0)	 125 (84.5) 16 (10.8) 7 (4.7)	0.993
ART (n, %) • FIVET/ICSI • IUI	23 (13.7) 21 (12.5) 2 (1.2)	4 (20.0) 4 (20.0) 0 (0)	19 (12.8) 17 (11.4) 2 (1.4)	0.382
Previous early miscarriage (n, %)	9 (5.3)	1 (5.0)	8 (5.4)	0.940
Smoking (n, %)	25 (14.9)	3 (15.0)	22 (14.9)	0.987
Surgical/histological diagnosis of endometriosis (n, %)	53 (31.5)	6 (30.0)	47 (31.8)	/
USG diagnosis of endometriosis (n,%)	149 (88.7)	17 (20)	132 (89.2)	/
Ovarian endometrioma, (n, %)	90 (53.6)	11 (55)	79 (53.4)	0.891
Rectovaginal endometriosis, (n,%)	71 (42.3)	9 (45)	62 (41.9)	0.792
Colorectal endometriosis, (n, %)	41 (24.4)	5 (25)	36 (24.3)	0.947
Uterosacral endometriotic nodule, (n, %)	22 (13.0)	3 (15)	19 (12.8)	0.788
Bladder endometriosis, (n, %)	2 (1.0)	0 (0)	2 (1.3)	0.601
1st and 2nd trimester variables				
PAPP-A (MoM, median, IQR)	0.84 (0.61-1.46)	0.61 (0.41-0.83)	0.88 (0.62-1.54)	<0.05
BhCG (MoM, median, IQR)	0.95 (0.63-1.45)	1.11 (0.89-1.45)	0.90 (0.58-1.44)	0.117
Mean UtA PI 1st trimester (median, IQR)	1.72 (±0.57)	2.23 (±0.63)	1.67 (±0.53)	<0.05
Mean UtA PI 2nd trimester (median, IQR)	0.98 (±0.30)	1.30 (±0.47)	0.94 (±0.28)	<0.05
Scan assessment during the 3rd trimester of pregnancy				
Gestational age 3rd trimester scan	31.6 (30.5-33.2)	31.5 (30.3-33.3)	31.6 (30.5-33.2)	0.889

EFW (g, mean, SD)	1848 (±304)	1661 (±265)	1873 (±301)	<0.05
EFW centile (mean, SD)	48.8 (±31.7)	29.0 (±20.9)	51.5 (±32.0)	<0.05
SGA fetuses (n,%)	30 (14.5)	6 (30)	16 (10.8)	<0.05
Pregnancy and perinatal outcome				
Gestational age delivery (median, IQR)	39.0 (38.1-40.4)	39.2 (38.2-39.8)	39.0 (38.1-40.5)	0.787
Birth Weight (mean, SD)	3264 (±528)	2883 (±397)	3315 (±523)	<0.05
Birth weight (centile, mean, SD)	46.2 (±29.1)	22.1 (±19.3)	49.4 (±28.7)	<0.05
SGA (n, %)	24 (14.3)	8 (40)	16 (10.8)	<0.05
5 minute Apgar <7 (n, %)	8 (4.8)	2 (10)	6 (4.1)	0.241
Preeclampsia (n, %)	16 (9.5)	4 (20)	12 (8.1)	0.089

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

Assisted Reproductive Technologies: ART; Endometriosis and Diffuse Adenomyosis: EDA; Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI

Table 2. Comparison between pregnant women with EFA and women with only endometriosis

	Total (n=186)	**EFA** (n =38)	**Only Endometriosis** (n =148)	**P value**
Demographics				
Maternal age (years, median, IQR)	30.0 (27.0-33.0)	30 (26.5-33)	30.0 (27.0-33.0)	0.849
Nulliparous (n,%)	159 (85.5)	36 (94.7)	123 (83.1)	0.069
BMI (kg/m^2, median, IQR)	23.9 (21-27,1)	25.2 (22.4-28.5)	23.7 (20.9-26.5)	0.265
Race (n,%) • Caucasian • Afro-Caribbean • Asian	156 (83.9) 21 (11.3) 9 (4.8)	31 (81.6) 5 (13.2) 2 (5.3)	125 (84.5) 16 (10.8) 7 (4.7)	0.907
ART (n,%) • FIVET/ICSI • IUI	25 (13.4) 21 (12.5) 2 (1.2)	6 (15.8) 6 (15.8) 0 (0)	19 (12.8) 17 (11.4) 2 (1.4)	0.634
Previous early miscarriage (n,%)	12 (6.5)	4 (10.5)	8 (5.4)	0.252
Smoking (n,%)	27 (14.5)	5 (13.2)	22 (14.9)	0.790
Surgical/histological diagnosis of endometriosis (n,%)	57 (30.6)	10 (26.3)	47 (31.8)	/
USG diagnosis of endometriosis (n,%)	149 (88.7)	17 (20)	132 (89.2)	/
Ovarian endometrioma, (n, %)	97 (52.2)	21 (55.3)	76 (51.4)	0.835
Rectovaginal endometriosis, (n,%)	77 (41.4)	15 (39.5)	62 (41.9)	0.787
Colorectal endometriosis, (n, %)	44 (23.7)	8 (21.0)	36 (24.3)	0.672
Uterosacral endometriotic nodule, (n, %)	25 (13.4)	6 (15.8)	19 (12.8)	0.634
Bladder endometriosis, (n, %)	2 (1.0)	0 (0)	2 (1.3)	0.471
1st and 2nd trimester variables				
PAPP-A (MoM, median, IQR)	0.86 (0.64-1.41)	0.84 (0.66-1.2)	0.88 (0.62-1.54)	0.286
BhCG (MoM, median, IQR)	0.90 (0.58-1.39)	0.88 (0.56-1.31)	0.90 (0.58-1.44)	0.725
Mean UtA PI 1st trimester (median, IQR)	1.67 (±0.50)	1.61 (±0.45)	1.67 (±0.53)	0.526
Mean UtA PI 2nd trimester (median, IQR)	0.93 (±0.27)	0.92 (±0.22)	0.94 (±0.28)	0.669
Scan assessment during the 3rd trimester of pregnancy				
Gestational age 3rd trimester scan	31.6 (33.2-30.5)	31.6 (33.2-30.5)	31.6 (30.5-33.2)	0.815
EFW (g, mean, SD)	1868 (±294)	1850 (±268)	1873 (±301)	0.671

EFW centile (mean, SD)	51.1 (±32.5)	49.6 (34.6)	51.5 (±32.0)	0.755
SGA fetuses (n, %)	30 (14.5)	8 (21.1)	16 (10.8)	0.093
Outcome at birth				
Gestational age delivery, (median, IQR)	39 (38.1-40.5)	39.4 (37.7-40.5)	39.0 (38.1-40.5)	0.573
Birth Weight (mean, SD)	3302 (±548)	3250 (±643)	3325 (±523)	0.517
Birth weight centile (mean, SD)	48.9 (±29.0)	46.7 (±30.5)	49.4 (±28.6)	0.613
SGA (n, %)	24 (12.9)	8 (21.1)	16 (10.8)	0.093
5 minute Apgar <7 (n, %)	8 (4.3)	2 (5.3)	6 (4.1)	0.743
Preeclampsia (n, %)	18 (9.7)	6 (15.8)	12 (8.1)	0.153

Data are shown as median (interquartile range), mean (standard deviation) or number (%).

Assisted Reproductive Technologies: ART; Endometriosis and Focal Adenomyosis: EFA; Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI

Table 3. Logistic regression analysis for prediction of SGA in patients with EDA

SGA (n)	OR	95% CI	p-value
BMI	1.033	0.938-1.138	0.507
PAPP-A (MoM)	1.254	0.551-2.857	0.590
Uterine Artery mean PI (2nd trimester)	4.887	1.287-18.566	0.020
Diffuse adenomyosis	3.902	1.161-13.110	0.028

Endometriosis and Diffuse Adenomyosis: EFA; Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI; Odds Ratio: OR

Table 4. Logistic regression analysis for prediction of SGA in patients with EFA

SGA (n)	OR	95% CI	p-value
BMI	0.987	0.900-1.082	0.776
PAPP-A (MoM)	0.681	0.289-1.607	0.381
Uterine Artery mean PI (2nd trimester)	0.424	0.068-2.632	0.357
Focal adenomyosis	2.048	0.793-5.289	0.139

Endometriosis and Focal Adenomyosis: EFA; Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI; Odds Ratio: OR