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Cervical length surveillance for predicting spontaneous preterm birth in women with uterine anomalies: a cohort study

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Conflicts of interest

None

ABSTRACT

Introduction: Uterine anomalies occur in an estimated 5% of women and have been shown to confer a higher risk of spontaneous preterm birth (SPTB). A sonographically short cervix (<25mm) is a risk indicator for SPTB, although its predictive utility has been little studied in this specific high-risk population. We aimed to assess the pregnancy outcomes and predictive ability of short cervix in a cohort of women with uterine anomalies attending a high-risk antenatal clinic. **Material and methods:** This historical cohort study assessed all pregnancies in women with congenital uterine anomalies referred to Preterm Labour Clinic at the Royal Women's Hospital, Melbourne, Australia between 2004 and 2013. Logistic and linear regressions and receiver-operator curves were used to examine associations between cervical length and preterm birth. **Results:** SPTB (<37 weeks' gestation) occurred in 23% of the 86 pregnancies (n=20); rates by subgroup were: unicornuate uterus 60% (n=3/5), uterus didelphys 40% (n=6/15), bicornuate uterus 18% (n=9/51), septate uterus 13% (n=2/15). Preterm prelabour rupture of membranes occurred in 55% of spontaneous preterm births, and was not independently associated with the presence of cervical cerclage or ureaplasma urealyticum. Short cervical length was associated with SPTB in women with septate uterus. Short cervix at 24 weeks (not at 16 or 20 weeks) was moderately predictive of SPTB <34 weeks. **Conclusions:** Women with uterine anomalies are at increased risk of spontaneous preterm birth, particularly those with unicornuate uterus or uterus didelphys, but cervical surveillance did not identify these cases. Short cervix may be associated with SPTB in women with septate uterus. Preterm prelabour rupture of membranes occurred in 55% of

SPTB. More research is required into aetiology to help determine appropriate monitoring and treatment.

Key words:

premature birth; uterine anomalies; ultrasonography, prenatal; cervix uteri; cervical length measurement.

Abbreviations

AUC area under the curve

CI confidence interval

RR relative risk

PPROM preterm prelabour rupture of membranes

SPTB spontaneous preterm birth

TVUS transvaginal ultrasound

Key message

Midtrimester transvaginal sonographic cervical length surveillance in women with uterine anomalies appears to predict spontaneous preterm birth only in those with a septate uterus. Preterm prelabour rupture of membranes occurs more frequently in women with uterine anomalies.

INTRODUCTION

Uterine anomalies arise during embryological development when Müllerian ducts – which constitute the basis of the uterus, fallopian tubes, cervix and upper two-thirds of the vagina – either fail to form, fuse, or resorb normally. A disruption in development results in a range of malformations that includes unicornuate, bicornuate, didelphys, septate and arcuate uterine morphology.

The presence of a uterine anomaly is a risk indicator for spontaneous preterm birth (SPTB),(1) but the mechanism by which this occurs is not understood. Current theories of the pathophysiology of preterm birth suggest that multiple aetiologies exist, including infection or inflammation,(2) vascular disorders, uterine overdistension, cervical disease, decidual senescence, decline in progesterone action, and breakdown of maternal-fetal tolerance.(3) It is possible, however, that the dominant pathway that triggers preterm labour in an abnormal uterus is different to those responsible in other high-risk groups, and may even vary among the different types of anomalies. A recent study of placental histopathology suggests placental malperfusion may precipitate around 20% of spontaneous preterm births in women with uterine anomalies.(4) Other potential functional effects of a uterine anomaly could include alteration in tissue stiffness resulting in early triggering of myometrial stretch receptors in a smaller or irregularly shaped uterine cavity (as described in the setting of multiple pregnancy and polyhydramnios), (3) differing distribution of progesterone receptors, or variation in uterine contractile signalling (5).

A short cervix during the second trimester, measured by transvaginal ultrasound (TVUS), is a well-established marker of an elevated SPTB risk (6-8), however it lacks specificity in the general antenatal population (7). Most previous research has focused on high-risk women, although study populations have typically comprised women with one or more different risk factors. The drawback of this approach is that it assumes all spontaneous preterm births occur as a result of an identical process, which may not be accurate. Therefore, cervical shortening may not be observed in all women who go on to birth prematurely,(9) and may be present in others to who go on to birth at or near term.

Few previous studies have specifically examined the role of cervical length surveillance in women with uterine anomalies. Airoldi and colleagues (10) reported on the outcome of 64 pregnancies in women with congenital uterine anomalies and found second trimester TVUS cervical length measurement <25mm was predictive of SPTB <35 weeks (relative risk (RR) 14, 95% confidence interval (CI) 3.5-54.7). Crane et al (11) studied 52 women with uterine anomalies, and reported that TVUS cervical length measurement <30mm was predictive of SPTB <35 weeks (odds ratio 62.1, 95% CI 5.7 - 676). Most recently, Ridout et al (12) describe outcomes from 319 women with uterine anomalies, in whom a short cervix <25mm did not predict SPTB < 37 or 34 weeks. When subgroup analysis was performed, however, short cervix was shown to predict SPTB in women with resorption defects (area under the

curve (AUC) 0.80, 95% CI 0.62 – 0.97 for women with septate uterus, AUC 0.83, 95% CI 0.51 to 0.98 for women with arcuate uterus), but not fusion defects.

The aim of the present study was to investigate the utility of TVUS cervical length surveillance in predicting preterm birth in women with congenital uterine anomalies.

MATERIAL AND METHODS

Participants

Data were collected on consecutive pregnancies in women with known congenital uterine anomalies attending the Preterm Labour Clinic of the Royal Women's Hospital (Melbourne, Australia) between 2004 and 2013. These were part of a larger historical cohort of women at high risk of preterm birth published previously (13). Women attended the clinic fortnightly between 14 and 26 weeks' gestation (or from gestational age at referral until 26 weeks), wherein TVUS cervical length surveillance was undertaken. TVUS cervical length measurement technique has been described previously (13). A minimum of two in-house TVUS cervical length measurements were required for inclusion, along with documentation or imaging confirming presence and classification of uterine anomaly according to the American Fertility Society system (see Figure 1).(14) If description of the uterine anomaly was conflicting, in-house imaging was considered diagnostic. TVUS was performed or supervised by an obstetrician experienced in transvaginal sonography, using a General Electric Logiq3 ultrasound machine (General Electric Healthcare, Fairfield, CT, USA). Where more than one cervical length measurement was available for a given week of gestation, the shortest was recorded for analysis. Women with cervical length < 25mm were offered preventive treatments as part of their care at the clinic, including vaginal progesterone or transvaginal cervical cerclage, following principles of shared decision making. Where cervical length measured < 15mm, cerclage would be recommended in addition to progesterone.

Cervical swabs were taken routinely at each visit as part of the clinic protocol. Antibiotic treatment was offered to women whose cultures returned microbes potentially associated with SPTB (erythromycin 250mg orally q6hrly for 10 days). Women who experienced preterm prelabour rupture of membranes (PPROM) prior to 32 weeks' gestation were treated with

broad-spectrum intravenous antibiotics (amoxicillin 2g IV q6hrly with erythromycin 250mg orally q6hrly for 48 hours, followed by amoxicillin 250mg orally q8hrly and erythromycin 500mg orally q8hrly for 5 days); those where PPROM occurred after 32 weeks were treated with erythromycin 250mg orally q6hrly according to hospital protocol.

Vaginal progesterone was prescribed as 200mg pessaries administered nocte. Cerclages were performed according to the McDonald technique, preferably under regional anaesthesia with perioperative antibiotic prophylaxis (15).

Exclusion criteria comprised medically indicated preterm birth, missing delivery data, or conflicting/unclear documentation of uterine anomaly. Women with an arcuate uterus were not referred to Preterm Labour Clinic due to conflicting reports about its impact on reproductive outcomes (1, 16).

Data were retrieved from the electronic pathology system and paper files, and entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA).

Statistical Analyses

Descriptive statistics were calculated in Excel for demographic data and cohort outcomes. Stata 13 (StataCorp LP, College Station, Texas, USA) was used for the remainder of statistical analysis.

Logistic and linear regressions (using the Firth correction for collinearity(17)) were used to investigate associations between cervical length, other potential predictive factors and SPTB. Receiver-operator curves were also used to evaluate the predictive ability of cervical length for SPTB at different thresholds. Kaplan-Meier curves were used to compare pregnancy outcomes between subgroups of women with different uterine anomaly types.

Ethical approval

This project was granted exemption from formal ethics review by the local institutional Human Research Ethics Committee, as it was deemed to meet the criteria established for quality assurance activities outlined in the National Health and Medical Research Committee guideline *Ethical Considerations in Quality Assurance and Evaluation Activities 2014* (18).

RESULTS

Data from 86 pregnancies were analysed, involving bicornuate uterus (n=51), septate uterus (n=15), uterus didelphys (n=15) and unicornuate uterus (n=5). Baseline descriptive statistics are summarised in Table 1. At least 73% of women had a uterine anomaly as their only risk factor for SPTB. SPTB <37 weeks' gestation occurred in 20 women (23%), and at <34 weeks in 11 women (13%). PPROM occurred in 55% of preterm births (11/20). Forty-nine women (57%) received treatment with erythromycin for colonisation with ureaplasma species. A short cervix </=25mm was identified in nine women (10%), of whom five went on to deliver prior to 37 weeks. Forty-six births were via caesarean section (54% of all births), primarily due to malpresentation (n= 31, 67% of caesareans) or as repeat procedures (n=7, 15%).

Cervical cerclage was utilised in five pregnancies (see also Table 1):

- Woman with septate uterus and history of midtrimester losses (elective)
- Same woman in a subsequent pregnancy (elective)
- Two women with uterus didelphys (ultrasound-indicated)
- Woman with bicornuate uterus (ultrasound-indicated)

Three of this group also utilised progesterone pessaries due to ongoing cervical shortening. Three of the five women with cerclage in situ delivered before 37 weeks, one of these prior to 34 weeks. An additional four women (two with bicornuate uterus, one with a septate uterus and previous septal excision, one with a subseptate uterus) were treated with vaginal progesterone alone, resulting in two term deliveries and one 36-week SPTB.

SPTB<37 weeks occurred most frequently in women with a unicornuate uterus (n= 3/5, 60%), followed by uterus didelphys (n=6/15, 40%), bicornuate (n=9/51, 18%) and septate uterus (n=2/15, 13.33%) respectively. Preterm birth <34 weeks occurred at equal rates in women with unicornuate uterus and uterus didelphys (20%), less commonly in those with a bicornuate uterus (9.8%). and not at all in women with a septate uterus. The gestations at delivery for each type of uterine anomaly are represented graphically in Kaplan Meier curves in Figure 2.

A short cervix (<25mm) at any time during the surveillance period was associated with SPTB <37 weeks (p=0.03, RR 2.9, 95% CI 1.2-6.7), but not SPTB <34 weeks (p=0.24, RR 2.4 95%

CI 0.56-10). When women who received progesterone or cerclage were excluded from analysis, the association was not strengthened (SPTB <37 weeks p=0.35, RR 4.1, 95% CI 0.27 – 62, SPTB <34 weeks p=0.18, RR 10, 95% CI 0.70 – 143). Receiver operator characteristic (ROC) analysis was performed for cervical length measurements at 16 weeks, 20 weeks and 24 weeks versus SPTB <37 week and <34 weeks (See Figure 3a and 3b). If no cervical length measurement was available at for a given gestational age, the measurement taken nearest to that time point was used. AUCs for SPTB < 37 weeks were 0.38, 0.48 and 0.56 for 16, 20 and 24 weeks respectively. This analysis showed short cervix at 24 weeks had some ability to predict SPTB <34 weeks, with AUC 0.75 (see Figure 4), while at 16 weeks and 20 weeks, AUCs were 0.47 and 0.55 respectively. This analysis was repeated on the cohort after excluding women who received progesterone or cerclage, with similar results (AUCs 0.34, 0.45, 0.77 for 16 weeks, 20 weeks and 24 weeks respectively).

Linear regression was also performed to examine for an association between shortest cervical length and gestational age at delivery, avoiding the pitfalls of dichotomisation.(19) When adjusted for smoking status, maternal age and parity, there was no association between cervical length and gestational age at delivery (p=0.12).

Separate univariate analysis was performed for each subgroup to assess for association between short cervix and STPB <37 and <34 weeks. Short cervix was associated with SPTB < 37 weeks for the septate uterus subgroup only (Fisher's exact, p=0.02), with RR=13 (95% CI 2.0 – 85, p=0.00). Insufficient numbers precluded subgroup analysis for STPB <34 weeks.

Univariate analysis was performed to investigate associations between potential predictive factors (smoking, cervical length <25mm, ureaplasma colonisation, conception with artificial reproductive technology) and SPTB (<37 weeks and <34 weeks). Variables yielding p < 0.1 on Fisher's exact test were entered into a logistic regression. No factor had a significant association with SPTB <37 or 34 weeks.

Ureaplasma colonization was not associated with PPROM or spontaneous preterm labour with intact membranes. Three women of the five with a cerclage experienced PPROM; this was a significant association with univariate analysis (Fisher's exact, p = 0.01, RR 6.1, 95%CI 2.3-16), but not logistic regression.

DISCUSSION

The main findings of this study include a confirmation of the known elevated rate of SPTB amongst women with uterine anomalies, the limited capacity of cervical length to predict SPTB in this group, and a relatively high rate of PPROM that appeared to be unrelated to either the use of cerclage or the presence of ureaplasma on cervical swabs.

The rate of preterm birth according to uterine anomaly is in keeping with other studies (1, 20), and thus the findings are useful for counselling women. A woman with a septate uterus, for example, can be advised that her risk of SPTB (in the absence of other risk factors) is approximately twice the background risk of 7% (21). Women with unicornuate uterus or uterus didelphys should be counselled about the high likelihood of preterm birth, although it appears that many of these are late preterm births.

The Kaplan-Meier curves show a small cluster of early SPTB in the bicornuate uterus group, all in women with normal cervical length. These three births all occurred following spontaneous preterm labour with intact membranes, including a 22-week loss with stage III chorioamnionitis on placental histopathology, a 23-week loss of a fetus with bilateral talipes equinovarus, and a 25-week SPTB in the setting of placental abruption. It is unclear whether the periviable losses were causally linked to the uterine anomaly, or due to unrelated factors.

Although an association was found between SPTB <37 weeks and a short cervix any time during the surveillance period, this was not present when controlling for other factors. Most notably, a short cervix at any of 16 weeks, 20 weeks or 24 weeks' gestation demonstrated no utility in predicting birth prior to 37 weeks in the cohort overall. The apparently stronger association between short cervix and SPTB in the septate uterus subgroup warrants further analysis, but small numbers precluded this. The larger study by Ridout et al (12) suggests that the association we found is valid and our study, although smaller, provides independent evidence supporting the other report.

The clinical implications of the above analyses are that, while women with uterine anomaly are at increased risk for SPTB, they may not benefit from cervical surveillance: a short cervix at 16 or 20 weeks had no association with SPTB, and measurement at 24 weeks had only a moderate association with SPTB before 34 weeks. Additionally, SPTB frequently occurred independently of a short cervix. A previous review of cervical surveillance versus single mid-trimester cervical length measurement in high-risk women found no improvement in prediction of SPTB, (22) instead favouring a single measurement between 18 and 24 weeks.

The value of this assessment depends on the existence of an effective therapy, however vaginal progesterone, the typical first-line treatment, has not been studied specifically in this population.

Cervical shortening has been extensively studied for its association with preterm birth in the high-risk antenatal population, however its positive predictive value is poor overall (7, 9) . A criticism of previous research in this area has been the heterogeneity of study groups (9). While this study does not entirely overcome that problem, this group of women had few other risk factors for preterm birth. A further strength of this study is the near-complete capture of women with known uterine anomalies attending for antenatal care during the study period, on account of hospital referral guidelines.

Given that other groups (10, 11) have found an association between short cervix and SPTB, we further examined our data with subgroup analysis by uterine anomaly type. This yielded a significant association between short cervix (<25mm) and SPTB only in women with a septate uterus (with the caveat that this group was extremely small and therefore prone to Type II error). We hypothesise that this is because the septate uterus is most similar both structurally and functionally to a normal uterus. Certainly, small numbers (n=5) in the unicornuate uterus group may account for the lack of association, which was contrary to that found by Airoldi et al (10) , who analysed a slightly larger subgroup of twelve women.

A shortcoming of our analysis, however, is that treatments for the prevention of SPTB (cervical cerclage, vaginal progesterone) were provided – albeit to only 10% of the study population, almost all of whom had a short cervix – but the data were analysed as though the treatments had no effect. Cerclage and progesterone may help stabilise or even lengthen the cervix (23), which could obscure or weaken an association (if it exists) between short cervix and SPTB in women with uterine anomaly. Conversely, SPTB may occur in women with uterine anomalies independently of cervical length, and it is possible these treatments may be less relevant in this subset of the high-risk population. We did, however, attempt to explore the influence of these treatments on our study group by excluding treated women from the analysis, without significant impact on the outcome.

Another limitation of this study is the small number of women with a short cervix. This increases the possibility of a type II error, in that an association between short cervix and SPTBcould truly exist, but could not be detected in this small group. However, a larger study (12) drew similar conclusions, adding weight to our findings.

PPROM occurred in 55% of all SPTB in this group of women with uterine anomalies, compared to 25-30% in a general high-risk antenatal population (24). PPROM has previously been observed to occur more frequently in this group, with an odds ratio of 6.3 (95% CI 3.0-13) in a historical case-control study of 729 women (20). PPROM is generally thought to have an infective or inflammatory aetiology (24), and an explanation for a higher prevalence in women with uterine anomalies is not presently available. The microbial link may be reflected in the high incidence of ureaplasma colonization noted in this group (28% compared to 15% in our previously published cohort of high-risk women(13)), yet this was not convincingly or independently associated with PPROM or SPTB. PPROM was associated with the presence of a cerclage, however whether this is a true difference between groups of such disparate size is unclear: it may simply represent the different risk profile of those women who underwent cerclage. The association did not persist on multivariate analysis, and is therefore in keeping with the conclusion of a recently updated Cochrane review, (25) which suggested that cervical cerclage did not increase the rate of PPROM.

CONCLUSION

Overall, cervical surveillance in women with uterine anomalies may not predict SPTB. However, a single TVUS cervical length measurement at 24 weeks' gestation may identify some women with uterine anomalies at risk of SPTB <34 weeks related to a short cervix. Additionally, women with septate uterus may benefit from cervical length screening or surveillance, as a significant association was found in this subgroup. While women with uterine anomalies, particularly unicornuate uterus or uterus didelphys, are at a significantly increased risk of SPTB, this may occur independently of cervical shortening by a mechanism that is not yet identified. An established preventive treatment for these women, whether the cervix is shortened or not, is lacking.

Women with uterine anomalies who deliver prematurely were more likely to do so in the setting of PPROM, and to have ureaplasma species present on cervical swab compared to a general high-risk population, although the significance of this is unclear. Ongoing research into methods of predicting preterm birth in this group of women, and the mechanism by which it occurs, will be of benefit in the future.

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Legends

Table 1. Characteristics of participants and outcomes.

Figure 1. American Fertility Society classification of uterine anomalies. Published with permission from Fertil Steril. 1988;49(6):944-55 ©Elsevier.

Figure 2. Kaplan-Meier survival curves for transvaginal ultrasound cervical length measurements at 16 weeks, 20 weeks, 24 weeks.

Figure 3a. Receiver-operator curve: cervical length at 16, 20 or 24 weeks predicting spontaneous preterm birth <37 weeks.

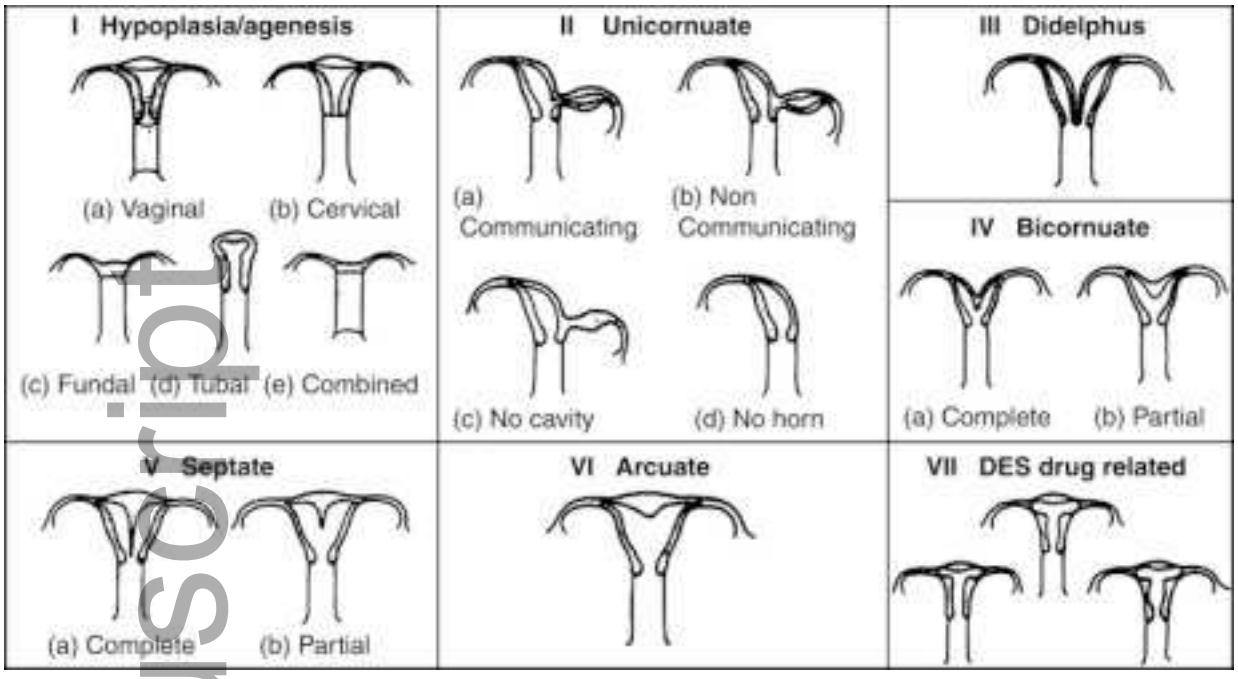
Figure 3b. Receiver-operator curve: cervical length at 16, 20 or 24 weeks predicting spontaneous preterm birth <34 weeks.

Figure 4. Receiver-operator curve: cervical length at 24 weeks predicting spontaneous preterm birth <34 weeks

Table 1. Characteristics of participants and outcomes.

Uterine anomaly type	**N**	**%**
Bicornuate	51	59.30
Septate	15	17.44
Uterus didelphys	15	17.44
Unicornuate uterus	5	5.81
Total	**86**	**100**
Short cervix	9	10.47
Treatment		
Progesterone	7	
Cerclage		
- Total	5	5.81
- Ultrasound-indicated	3	3.48
Delivery outcomes		
SPTB <37/40	20	23.36
SPTB <34/40	11	12.79
PPROM	11	55% of SPTB
Preterm labour with intact membranes	9	45% of SPTB
Mode of delivery		
Caesarean section	46	53.49
Vaginal birth	40	46.51

SPTB, spontaneous preterm birth; PPROM, preterm prelabour rupture of membranes.



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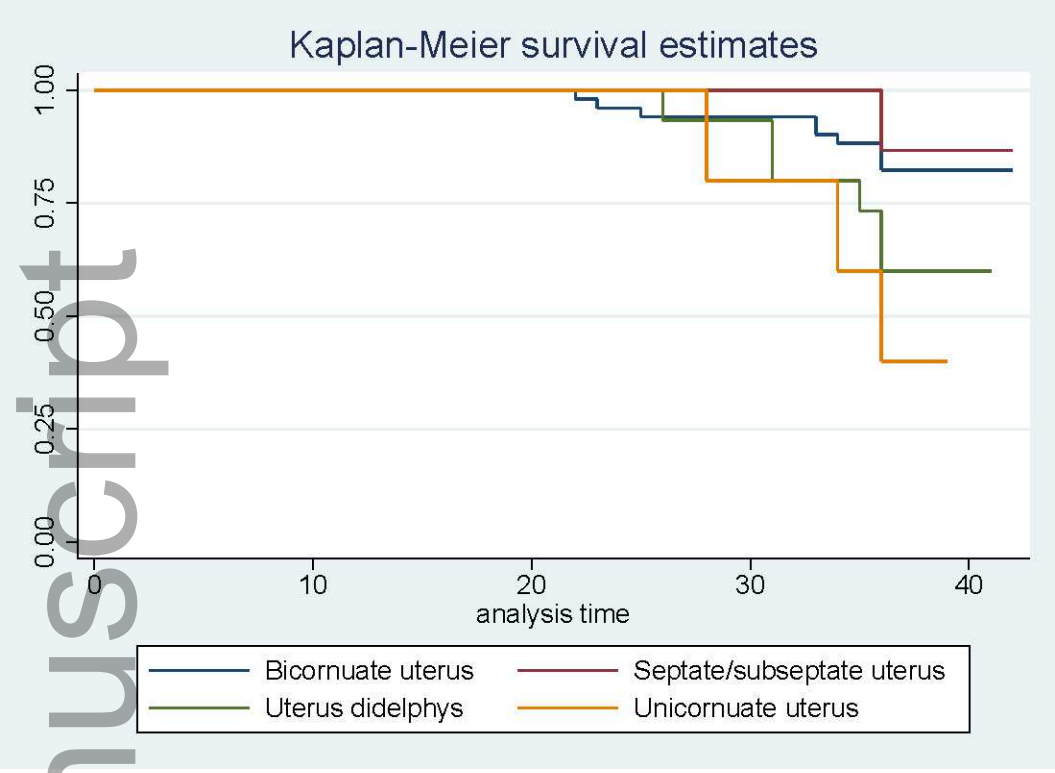

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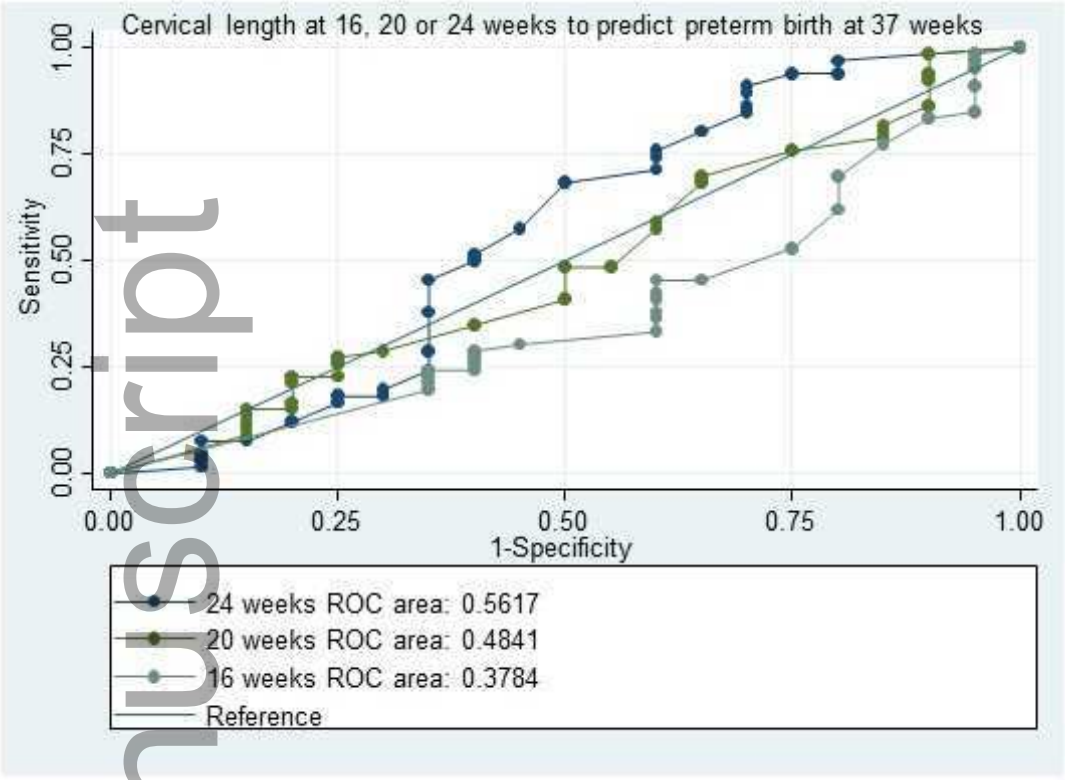


Figure 3a: Ability of cervical length measured at early, middle and late second trimester to predict SPTB at 37 weeks.

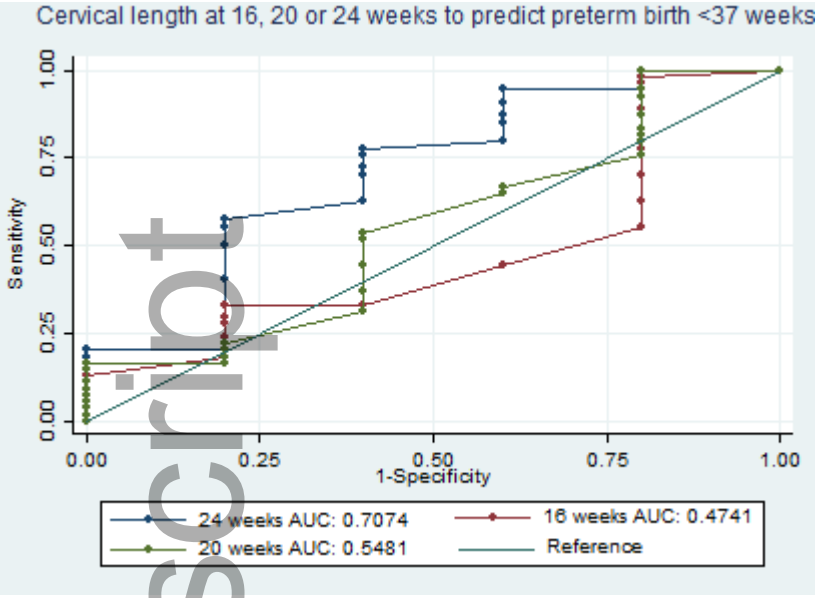
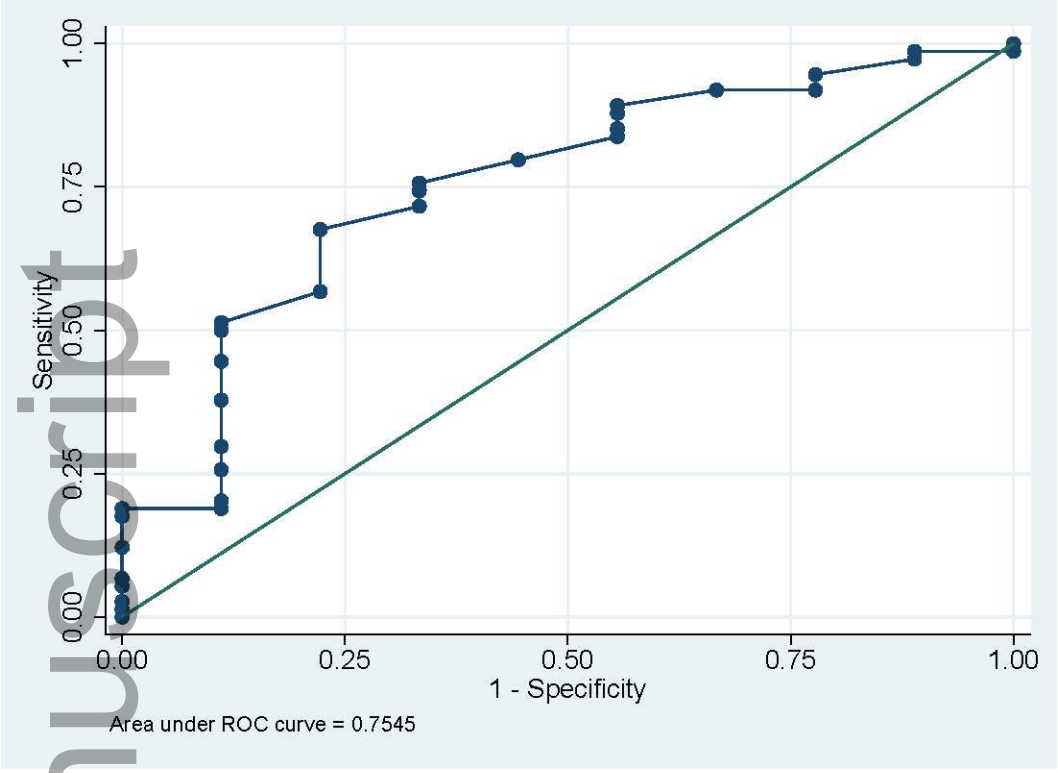


Figure 3b: Ability of cervical length measured at early, middle and late second trimester to predict SPTB at 34 weeks.



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