OBSTETRICS

Cervical length and quantitative fetal fibronectin in the prediction of spontaneous preterm birth in asymptomatic women with congenital uterine anomaly

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BACKGROUND: Congenital uterine anomalies are associated with late miscarriage and spontaneous preterm birth.

OBJECTIVE: Our aim was 1) to determine the rate of spontaneous preterm birth in each type of congenital uterine anomaly, and 2) to assess the performance of quantitative fetal fibronectin and cervical length measurement by transvaginal ultrasound in asymptomatic women with congenital uterine anomalies for the prediction of spontaneous preterm birth at <34 and <37 weeks of gestation.

MATERIALS AND METHODS: This was a retrospective cohort of women with congenital uterine anomalies asymptomatic for spontaneous preterm birth, from 4 tertiary referral centers in the United Kingdom (2001–2016). Congenital uterine anomalies were categorized into fusion (unicornuate, didelphic, and bicornuate uteri) or resorption defects (septate, with or without resection, and arcuate uteri), based on pre-pregnancy diagnosis. All women underwent serial transvaginal ultrasound cervical length assessment in the second trimester (16 to 24 weeks' gestation); a subgroup underwent quantitative fetal fibronectin testing from 18 weeks' gestation. We investigated the relationship between congenital uterine anomalies and predictive test performance for spontaneous preterm birth at <34 and <37 weeks' gestation.

RESULTS: A total of 319 women were identified as having congenital uterine anomalies in our high-risk population. Of the women, 7% (23/319) delivered spontaneously at <34 weeks' gestation and 18% (56/319) at <37 weeks' gestation. Rates of spontaneous preterm birth by type were as follows: 26% (7/27) for unicornuate, 21% (7/34) for didelphic, 16% (31/189) for bicornuate, 13% (7/56) for septate, and 31% (4/13) for arcuate. In all, 80% (45/56) of women who had spontaneous preterm birth at <37 weeks did not develop a short cervical length (<25 mm) during the surveillance period (16–24 weeks). The diagnostic accuracy of short cervical length had a low sensitivity (20.3) for predicting spontaneous preterm birth at <34 weeks. Cervical length had an area under the receiver operating curve of 0.56 (95% confidence interval, 0.48–0.64) and 0.59 (95% confidence interval, 0.55–0.64) for prediction of spontaneous preterm birth at <34 and <37 weeks, respectively. The area under the curve for cervical length to predict spontaneous preterm birth at <34 weeks was 0.48 for fusion defects (95% confidence interval, 0.39–0.57) but 0.78 (95% confidence interval, 0.66–0.91) for women with resorption defects. Overall quantitative fetal fibronectin had an area under the curve of 0.63 (95% confidence interval, 0.49–0.77) and 0.58 (95% confidence interval, 0.49– 0.68) for prediction of spontaneous preterm birth at <34 and <37 weeks, respectively. The area under the curve for prediction of spontaneous preterm birth at <37 weeks with quantitative fetal fibronectin for fusion defects was 0.52 (95% confidence interval, 0.41–0.63) but 0.79 (95% confidence interval, 0.63–0.95) for women with resorption defects. Results were similar when women with intervention were excluded.

CONCLUSION: The commonly used markers cervical length and quantitative fetal fibronectin have utility in prediction of spontaneous preterm birth in resorption congenital uterine defects but not in fusion defects. This is contrary to findings in other high-risk populations. These findings need to be accounted for when planning antenatal care, and have potential implications for predictive tests used in spontaneous preterm birth surveillance and intervention.

Key words: bicornuate, canalisation defects, cervical length, congenital uterine anomaly, fetal fibronectin, fusion defect, preterm birth, resorption defect, unicornuate, unification defects, uterus didelphys

The presence of a congenital uterine anomaly (CUA) is a well-established cause of pregnancy complications, including infertility, recurrent first- and second-trimester miscarriages, preterm birth (PTB) with or without preterm premature rupture of the membranes (PPROM), as well as intrauterine growth restriction, fetal malposition and caesarean section.[1–4] The types of CUA are individually associated with varying degrees of adverse outcomes.

Formation of the female reproductive tract involves a chain of complex steps, with differentiation, migration, unification, and subsequent canalization of the Müllerian ducts.[5] A deviation anywhere along this stepwise development pathway will result in a CUA, ranging from arcuate uterus, a subtle variation from normal anatomy, to complete failure of fusion of the Müllerian ducts, with 2 discrete cervical canals and uterine cavities (uterus didelphys). Recognition of CUA is often noted only in the presence of pathology, for example, recurrent miscarriage or early delivery. However, in women with recurrent pregnancy loss, the rate can be as high as 10%.[6,7]

Although specific CUAs differ in rates of spontaneous preterm birth (sPTB), and reliable control data to quantify this are lacking, all are associated with poor

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AJOG at a Glance

Why was this study conducted?

- To assess the performance of current predictive markers of spontaneous preterm birth (sPTB), quantitative fetal fibronectin (qfFN), and transvaginal cervical length (CL) measurement in asymptomatic high-risk women with congenital uterine anomaly (CUA).
- To characterize rates of early delivery by type of CUA.

Key findings

- CUA, particularly fusion defects, are associated with high rates of late miscarriage and preterm birth.
- CL and qfFN have utility in prediction of sPTB in women with resorption defects but were no better than chance in women with fusion defects. This is contrary to other high-risk populations.

What does this add to what is known?

These findings need to be accounted for when planning antenatal care, and have potential implications for the predictive tests used in sPTB surveillance and intervention.

reproductive outcomes,[2] emphasizing the clinical importance of antenatal surveillance for this group. Identifying those women most at risk for sPTB is the strategy currently employed globally. The value of quantitative fetal fibronectin (qfFN) and cervical length (CL) have been proved in large prospective cohorts;[8–10] however, reports have concentrated on asymptomatic singletons with prior preterm birth, late miscarriage, or cervical surgery. There is limited evidence to support the use of predictive markers in women with CUAs.

We prospectively collected serial CL and qfFN data from a large cohort of high-risk women with CUAs who were asymptomatic for sPTB. Our aim was to determine the clinical utility of currently used predictive markers of sPTB in this group.

Study design

This is a retrospective cohort study of prospectively collected data from asymptomatic pregnant women with CUAs presenting to high-risk preterm surveillance clinics at 4 tertiary referral hospitals in London (Queen Charlotte's and Chelsea Hospital, St Thomas' Hospital, Chelsea and Westminster Hospital, and University College London Hospital), over a 15-year period (2001–2016). Women were included if the diagnosis of a CUA (unicornuate, didelphyic, bicornuate, septate, or arcuate) was made before pregnancy by imaging or surgery and classified according to the American Fertility Society classification (AFS; 1988) (currently the American Society of Reproductive Medicine). Surgical repair was recorded, as were any additional referral risk factors (1 or more previous sPTB or PPROM), previous late miscarriage ($14–23^{+6}$ weeks), or previous cervical surgery.

As part of routine clinical care within the preterm surveillance clinics, women underwent serial transvaginal ultrasound (TVUS) surveillance of CL between 16 and 24 weeks (second-trimester screening). Frequency of surveillance (TVUS and qfFN) varied between 2 and 4 weeks according to clinical need and continued until 24 weeks, independent of prophylactic intervention (cerclage and/or progesterone). Elective cervical cerclage was offered as per contemporaneous clinical practice based on the woman's previous obstetric history or ultrasound indicated cerclage based on a short CL in the index pregnancy defined as a CL <25 mm at <24 weeks' gestation. In a subgroup of women, qfFN measurement was carried out at each visit just before ultrasound, between 18 and 24 weeks' gestation. qfFN samples from women who reported sexual intercourse within 24 hours or with frank bleeding were excluded from the analysis according to manufacturer's instructions (Hologic Inc, Danbury, CT).

Maternal demographic data, serial CL and qfFN measurements, and maternal and neonatal outcome details were analyzed. Women were considered to have had a spontaneous preterm birth if they had spontaneous onset of labor, or experienced PPROM and delivered prematurely, regardless of mode of delivery. Women with iatrogenic delivery before the gestational time point of interest, twin pregnancies, and those with incomplete outcome data were excluded from the analysis. We repeated the analysis excluding women with intervention in situ.

This study was exempt from requiring ethical approval under the UK Health and Social Care Act 2012, which states that research involving anonymized, routinely collected clinical data is excluded from research ethics committee review.

Technique for qfFN measurement

During speculum examination, a polyester swab was inserted into the posterior fornix of the vagina (10 seconds) to collect a sample of cervicovaginal fluid. The swab was placed into the test buffer solution and analyzed immediately. An aliquot (200 μm) of the sample was analyzed using the quantitative Rapid fFN 10Q analyzer (Hologic, Marlborough, MA) according to manufacturer's instructions. All clinicians received appropriate training to use the analyzers.

Thresholds of 10 (lower limit of test), 50 (previous standard), and 200 ng/mL (based on existing literature) were predefined. The qfFN assay results are reported in units of nanograms per millilitre (ng/mL), and the result was standardized using purified fetal fibronectin and A128 measurement with an extinction coefficient of 1.28. The

TABLE 1
Spontaneous preterm birth in women with congenital uterine anomalies

Pregnancy outcome	Cohort (n =319)	Unicornuate (n = 27)	Didelphys (n = 34)	Bicornuate (n = 189)	Septate (n = 56)	Arcuate (n = 13)
sPTB at <37 wk	17.6% (56)	25.9% (7)	20.6% (7)	16.4% (31)	12.5% (7)	30.8% (4)
sPTB at <34 wk	7.2% (23)	3.7% (1)	8.8% (3)	6.3% (12)	5.4% (3)	30.8% (4)
sPTB at <37 wk when CUA is the sole risk factor	12.8% (33/257)	26.9% (7/26)	20.0% (6/30)	9.1% (13/143)	12.5% (6/48)	10% (1/10)

CUA, congenital uterine anomaly; *sPTB*, spontaneous preterm birth.
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reliability of the Rapid 10Q analyzer has previously been reported. For the 10Q Assay, the intraassay coefficient of variation is 5.7−7.3% and the intraassay coefficient of variation is 5.9−7.5%. Experiments that were performed during product development confirmed a good correlation between enzyme-linked immunosorbent assay and 10Q tests (slope = 0.97; $r^2 = 0.82$) (personal communication, Jerome Lapointe, Hologic Inc).

Technique for cervical length assessment

Serial CL assessment was undertaken in accordance with standardized guidelines by trained operators.[11,12] In summary, the woman was asked to empty her bladder, and then the TVUS probe was inserted into the anterior fornix of the vagina to obtain a sagittal long-axis view of the echogenic endocervical mucosa along the length of the cervical canal, allowing identification of both the internal and external os. Without causing undue pressure on the cervix with the probe to avoid falsely elongating it, the linear distance between the external and internal os in millimeters was recorded 3 times over a minimum of 3 minutes using optimal magnification and zoom settings, and the shortest CL was recorded. Transfundal pressure was exerted for 15 seconds. and subsequent demonstration of a cervical funnel was noted if present. The shortest total closed CL of 3 measurements was considered the length for analysis, with "short" CL defined as <25 mm.

Statistical analysis

Descriptive statistics were used to depict the study population. Predictive statistics were carried out to determine whether predictive tests (CL and qfFN) accurately predicted sPTB at <34 and <37 weeks' gestation. Statistical analysis was performed using Stata 14.0. Receiver operating characteristic (ROC) curves were generated and compared. Data from repeated sampling of the same individuals were analyzed. Therefore clustered bootstrapping with bias correction was used to

TABLE 2
Maternal characteristics of women with congenital uterine anomalies

Maternal characteristic, % (n)	Cohort (n=319)	Unicornuate (8.5%, 27)	Didelphys (10.7%, 34)	Bicornuate (59.3%, 189)	Septate (17.6%, 56)	Arcuate (4%, 13)
Primiparous	55.2% (176)	66.7% (18)	67.6% (23)	47.6% (90)	66.1% (37)	61.5% (8)
Multiparous	44.8% (143)	33.3% (9)	32.4% (11)	52.4% (99)	33.9% (19)	38.5% (5)
Previous term delivery	35.0% (50/143)	22.2% (2/9)	36.4% (4/11)	38.4% (38/99)	26.3% (5/19)	20% (1/5)
Previous first-trimester miscarriage	31.9% (61/191)	30.8% (4/13)	30.4% (7/23)	29.9% (35/117)	41.7% (15/36)	0% (0/2)
Previous sPTB at <37 wk	15.9% (45/283)	0% (0/22)	12.5% (4/32)	20.8% (36/173)	8.5% (4/47)	11.1% (1/9)
Previous mid-trimester loss	9.2% (26/283)	4.5% (1/22)	3.1% (1/32)	10.4% (18/173)	8.5% (4/47)	22.2% (2/9)
Previous cervical surgery	13.1% (37/283)	9.1% (2/22)	3.1% (1/32)	14.5% (25/173)	14.9% (7/47)	22.2% (2/9)
Ethnicity White Asian Black Unknown	48.6% (155) 3.4% (11) 5.3% (17) 42.6% (136)	8.4% (13) 18.1% (2) 0 8.8% (12)	11.6% (18) 18.1% (2) 0 10.3% (14)	58.1% (90) 36.3% (4) 82.4% (14) 60.0% (81)	17.4% (27) 27.3% (3) 5.9% (1) 18.4% (25)	5.0% (7) 0 11.8% (2) 2.9% (4)
BMI (median, IQR)	23.1 21.0 − 39.0	23.5 22.3 − 30.0	24.0 22.4− 33.8	23.0 20.9 − 39.0	23.0 20.6-36.8	23.9 21.0 − 36.7

Results given as percentage (number) or median and interquartile range.

BMI, body mass index; *IQR*, interquartile range; *sPTB*, spontaneous preterm birth.
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TABLE 3
Accuracy of quantitative fetal fibronectin and cervical length for the prediction of spontaneous preterm birth

	CL prediction		qfFN prediction	
Type of anomaly	ROC AUC, 95% CI		ROC AUC, 95% CI	
Whole cohort (N = 319)				
sPTB at <34 wk	0.56	0.48–0.64	0.63	0.49–0.77
sPTB at <37wk	0.59	0.55–0.64	0.58	0.49–0.68
Fusion defects				
sPTB at <34 wk	0.48	0.39–0.57	0.55	0.39–0.70
sPTB at <37 wk	0.60	0.55–0.65	0.52	0.41–0.63
Resorption defects				
sPTB at <34 wk	0.78	0.66–0.91	0.83	0.62–1.00
sPTB at <37 wk	0.66	0.55–0.78	0.79	0.63–0.95

AUC, area under the curve; *CI*, confidence interval; *CL*, cervical length; *qfFN*, quantitative fetal fibronectin; *ROC*, receiver operating characteristic; *sPTB*, spontaneous preterm birth.

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calculate confidence intervals for ROC curves.[13] qfFN analysis was carried out for a subgroup of women. Because of sample size, descriptive data alone were generated for this group.

Results

A total of 429 women with congenital uterine anomalies were identified in the 4 high-risk preterm surveillance clinics. Of these, 110 women were subsequently excluded from analysis as a result of missing outcome data/uterine anomaly classification (n = 91), multiple pregnancy (n = 9), and incomplete qfFN or CL data (n = 10).

Of the women included in the analysis (n = 319), 9% (27) had unicornuate, 11% (34) didelphic, 59% (189) bicornuate, 18% (56) septate, and 4% (13) arcuate uteri. The rate of sPTB at <37 weeks according to the type of CUA was 26% (7/27) of women with unicornuate, 21% (7/34) with didelphic, 16% (31/189) with bicornuate, 13% (7/56) with septate, and 31% (4/13) with arcuate uteri. Overall, the sPTB rate was 7% (23/319) at <34 weeks and 18% (56/319) at <37 weeks' gestation.

A total of 257 women (81%, 257/319) had CUA as their sole risk factor (ie, no additional history of sPTB/late miscarriage or cervical surgery). Rates of sPTB at <37 weeks for this group were as follows: 27% (7/26) for unicornuate, 20% (6/30) for didelphic, 9% (13/143) for bicornuate, 13% (6/48) for septate, and 10% (1/10) for women with an arcuate uterus (Table 1).

Women with septate uteri had a high rate of previous first-trimester miscarriage (42%, 15/36). One-fifth (21%, 36/173) of the women with bicornuate uteri had a previous history of sPTB. More than 20% (2/9) of the cohort with arcuate uteri had a history of 1 or more previous late miscarriages. Maternal characteristics relevant to risk of sPTB are shown in Table 2.

The incidence of sPTB at <34 and <37 weeks was 7% (23/319) and 18% (56/319), although when categorized by anomaly type, this increased to 26% (7/27) for unicornuate and 31% (4/13) for women with an arcuate uterus at <37 weeks (Table 1).

Cervical length assessment

In all, 319 women underwent a total of 955 TVUS CL measurements. On average, each women had 2.2 measurements per pregnancy (range 1–6). Of the women in this high-risk population, 29 (9%) were found to have a short CL (<25 mm), of whom 48% (14/29) delivered at <37 weeks.

Cervical length was a poor predictor of sPTB at <34 and <37 weeks' gestation

FIGURE 1
Transvaginal ultrasound cervical length to predict spontaneous preterm birth at <34 weeks in women with congenital uterine anomalies, grouped by fusion or resorption defect

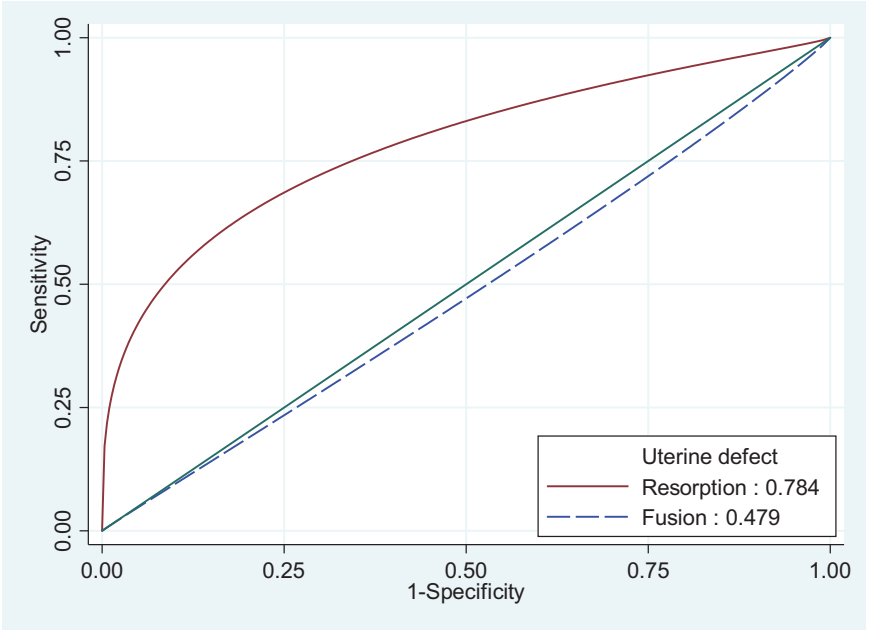

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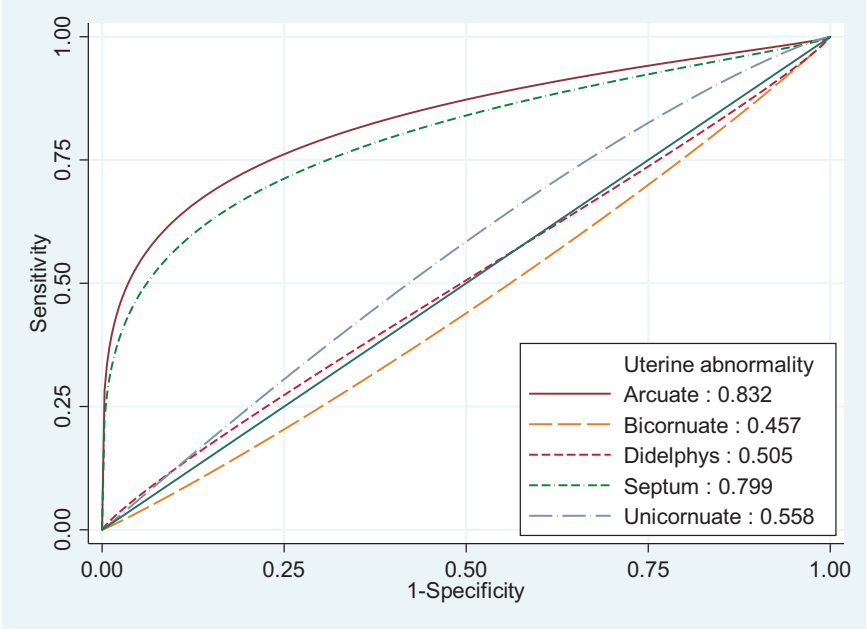
FIGURE 2
Transvaginal ultrasound cervical length to predict spontaneous preterm birth at <34 weeks, by type of congenital uterine anomaly defect. *Using binomial modeling



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when the cohort was analyzed as a whole (area under the curve [AUC], 0.56 [95% confidence interval {CI}, 0.48−0.64] and 0.59 [95% CI, 0.55−0.64], respectively) (Table 3), with a low diagnostic sensitivity when a cutoff of <25 mm was used (20.3 and 15.2 for sPTB at <34 and <37 weeks' gestation, respectively).

However, when the cohort was grouped according to fusion or resorption defects, CL behaved predictably for sPTB at <34 weeks in women with resorption (AUC, 0.78 [95% CI, 0.66−0.91]) but not fusion defects (AUC, 0.48 [95% CI, 0.39−0.57]) (Figure 1).

Cervical length was predictive for sPTB at <34 weeks in women with septate uteri (AUC, 0.80 [95% CI, 0.62−0.97) (Figure 2) (CL <25 mm: sensitivity 50.0), and in the arcuate group for delivery at <34 and <37 weeks (AUC, 0.83 [95% CI, 0.51−0.98]; sensitivity, 30.0). Results did not change after exclusion of women with intervention (septate excluding cervical cerclage: AUC, 0.85 [95% CI, 0.79−0.91]).

Prediction of sPTB at <34 and <37 weeks was poor in women with fusion defects (AUC, 0.48 [95% CI, 0.39−0.57] and AUC, 0.60 [95% CI, 0.55−0.65]) (Figure 1). For specific fusion defects, CL was also not predictive of sPTB at <37 weeks (unicornuate, 0.48 [95% CI, 0.34− 0.62], didelphic, 0.55 [95% CI, 0.42−0.68], and 0.62 [95% CI, 0.56−0.69) for bicornuate uteri). Diagnostic accuracy for individual CUA defects can be seen in Table 4.

Results were similar after excluding women with intervention (cerclage and/or progesterone) (unicornuate, 0.55 [95% CI, 0.39−0.74; didelphic, 0.55 [95% CI, 0.34−0.70; and bicornuate uteri, 0.62 [95% CI, 0.51−0.72]).

Quantitative fetal fibronectin

A total of 155 women underwent 793 cervicovaginal qfFN protein analysis. Overall qfFN had a ROC AUC of 0.63 (95% CI, 0.49−0.77) and 0.58 (95% CI, 0.49−0.68) for prediction of sPTB at <34 and <37 weeks, respectively.

We found qfFN to be an accurate test of sPTB at <34 and <37 weeks in women with resorption defects (AUC, 0.83 [95% CI, 0.62−1.00] and AUC, 0.79 [95% CI, 0.63−0.95], respectively) (Figure 3). This did not hold true for fusion defects (AUC for sPTB at <37 weeks, 0.52 [95% CI, 0.41−0.63]).

Management

More than half of the women in our cohort delivered by cesarean delivery (56%, 124/221), with the highest number in those women with didelphic (77%, 17/22) and unicornuate uteri (73%, 16/22). In all, 60% (9/15) of women with uterus didelphys had a fetal malposition at time of delivery (Table 5). In total, 11% (35/319) of women had a cervical cerclage during their pregnancy. A total of 51% (18/35) were ultrasound indicated, based on a CL of <25 mm at <24 weeks' gestation. Of the women, 11% were prescribed progesterone during their pregnancy, although we have data only on progesterone prescribing practices for 138 of 319 women (Table 6). In all, 80% (45/56) of women who delivered spontaneously at <37 weeks' gestation did not develop a short CL during our surveillance period (16−24 weeks' gestation).

Comment

Principal findings

This study showed that the commonly used markers CL and qfFN have utility in prediction of sPTB in resorption congenital uterine defects but not in fusion defects. This is contrary to other high-risk populations. In all, 80% (45/56) of women who went into spontaneous labor preterm did not develop a short CL during the antenatal surveillance period.

In our cohort, 21% (7/34) of women with a didelphic uterus (a fusion defect) delivered at <37 weeks' gestation, and 8% (3/34) at <34 weeks' gestation. Early pregnancy CL measurement was no better than chance at predicting delivery at <37 weeks, with poor AUC, sensitivity, and negative predictive value.

Asymptomatic qfFN screening in our whole cohort was a poor predictor of delivery at <34 weeks' gestation.

TABLE 4
Accuracy of cervical length for the prediction of spontaneous preterm birth in patient subgroups

Type of anomaly	ROC AUC, 95% CI	
Unicornuate (n = 27)		
sPTB <34 wk	0.56	0.32–0.80
sPTB <37 wk	0.48	0.34–0.62
Didelphys (n = 34)		
sPTB <34 wk	0.50	0.31–0.70
sPTB <37 wk	0.55	0.42–0.68
Bicornuate (n = 189)		
sPTB <34 wk	0.46	0.35–0.56
sPTB <37 wk	0.62	0.56–0.69
Septate (n = 56)		
sPTB <34 wk	0.80	0.62–0.97
sPTB <37 wk	0.61	0.47–0.76
Arcuate (n = 13)		
sPTB <34 wk	0.79	0.51–0.98
sPTB <37 wk	0.79	0.51–0.98

AUC, area under the curve; *CI*, confidence interval; *ROC*, receiver operating characteristic; *sPTB*, spontaneous preterm birth.
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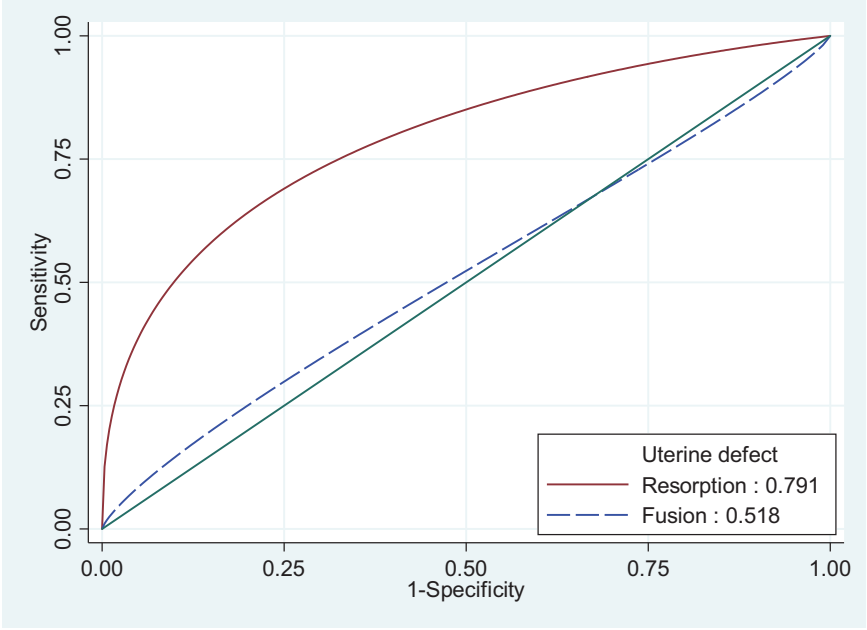
FIGURE 3
Quantitative fetal fibronectin to predict spontaneous preterm birth at <37 weeks, grouped by fusion or resorption defect



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This was confirmed for fusion defects (<34 weeks AUC, 0.55 [95% CI, 0.39–0.70; <37 weeks AUC, 0.52 [95% CI, 0.41–0.63]). This is contrary to other cohorts at high risk for sPTB (eg, history of late miscarriage), and therefore it is important that clinicians are aware of this when planning antenatal surveillance and choosing predictive tests for sPTB.

Clinical implications

Although women with CUA are considered to be at high-risk for sPTB, data correlating individual congenital uterine anomaly and outcome are limited. The existing strategy used for prediction of sPTB in women at high risk for other reasons is recognized to be inadequate. An understanding of the increased risk posed to women with each type of anomaly will help to determine their subsequent antenatal management pathways and the appropriate diagnostic tests. In this study, we report the accuracy of predictive markers of sPTB in asymptomatic high-risk women with CUA, correlating both CL and qfFN with individual defect types and categorized according to resorption or fusion defects.

The pathophysiological processes underlying early delivery in CUA cases remain uncertain. Deficiency in the endometrium overlying any anatomical variation, for example the septum, may provide a suboptimal site for implantation, disorderly and decreased blood supply insufficient to support placentation[14] and embryonic growth. Other potential hypothesized mechanisms include abnormal myometrial architecture producing uncoordinated uterine contractions[15] or reduced uterine capacity,[16] affecting stretch. The structure of the cervix is integral to the maintenance of pregnancy[17]; disruption in cervical architecture, particularly the internal cervical os, may account for increased rates of sPTB.

The difference in predictive test performance between fusion and resorption groups may be related to the underlying mechanism of preterm birth. In women with resorption defects (septate and arcuate uterus), predictive markers performed as seen in other high-risk

TABLE 5
Pregnancy outcomes in women with congenital uterine anomalies

Pregnancy outcome	Cohort (n = 319)	Unicornuate (n = 27)	Didelphys (n = 34)	Bicornuate (n = 189)	Septate (n = 56)	Arcuate (n = 13)
Primiparous women with sPTB at <37 wk	13% (22)	17% (3)	26% (6)	8% (7)	14% (5)	13% (1)
Multiparous women with sPTB at <37 wk	23% (33)	44% (4)	0% (0)	27% (24)	11% (2)	60% (3)
Rate of cesarean delivery	56% (124/221)	72.7% (16/22)	77.3% (17/22)	55.6% (70/126)	42.1% (16/38)	38.5% (5/13)
Fetal malposition	32% (39/121)	30.8% (4/13)	60% (9/15)	30.8% (16/52)	35.7% (10/28)	0% (0/13)
NICU admission	16% (20/123)	25% (1/4)	0% (0/12)	15.6% (12/77)	20% (4/20)	30% (3/10)

NICU, neonatal intensive care unit; sPTB, spontaneous preterm birth.

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populations: both CL and qfFN were useful predictors of sPTB at <34 and <37 weeks' gestation. Resorption defects have relatively normal uterine architecture. By definition, an arcuate uterus has an intrauterine indentation of <1 cm, and therefore it is plausible that it does not have an impact on either the cause of preterm delivery or the mechanism by which markers CL and qfFN predict delivery.

For more severe structural anomalies, such as unicornuate or uterus didelphys, the converse is likely to be true, and poor pregnancy outcome is hypothesized to be related to stretch effects secondary to altered uterine architecture, decreased muscle mass and abnormal cervical architecture, with or without abnormal uterine vasculature.[18] If the cervix plays no part in the etiology of labor onset, it may not predict delivery in this group. Further research needs to focus on novel predictive markers in this high-risk group.

Late miscarriage and preterm birth are frequently thought to be associated with inflammation and infection. Recent literature has linked true positive fFN results with placental inflammation, hypothesized to disturb the decidua–chorionic interface, threatening the integrity of the maternal–fetal interface, and leading to the release of fFN into the cervico-vaginal secretions where it is detected.[19] Quantitative fFN is a leading predictor of sPTB and its value as a screening tool for high-risk asymptomatic women is increasingly recognized.[8] However, abnormal myometrium and stretch effects may not cause this same release of fFN, which may account for its poor predictive value in fusion defects.

Study strengths and weaknesses

Three previous studies have reported the use of CL measurement in women with CUA,[20–22] and 1 study has evaluated the addition of qualitative fFN.[23] There was

TABLE 6
Antenatal management in asymptomatic women with congenital uterine anomalies

Pregnancy outcome	Cohort (n = 319)	Unicornuate (n = 27)	Didelphys (n = 34)	Bicornuate (n = 189)	Septate (n = 56)	Arcuate (n = 13)
Cerclage	11.0% (35/319)	11.1% (3/27)	14.7% (5/34)	10.1% (19/189)	12.5% (7/56)	7.7% (1/13)
Ultrasound indicated	51.4% (18/35)	7.4% (2/27)	5.8% (2/34)	5.8% (11/189)	3.6% (2/56)	7.7% (1/13)
sPTB at <37/40 wk	23.5% (5/18)	0% (0/2)	50% (1/2)	(5/11)	50% (1/2)	100% (1/1)
sPTB at <34/40 wk	23.5% (5/18)	50% (1/2)	50% (1/2)	(1/11)	50% (1/2)	100% (1/1)
History indicated	48.6% (17/35)	3.7% (1/27)	8.8% (3/34)	4.2% (8/189)	8.9% (5/56)	0% (0/13)
sPTB at <37/40 wk	23.5% (4/17)	0% (0/1)	33.3% (1/3)	25% (2/8)	20% (1/5)	0% (0/13)
sPTB at <34/40 wk	17.6% (3/17)	0% (0/1)	33.3% (1/3)	12.5% (1/8)	20% (1/5)	0% (0/13)
sPTB without short CL	80.4% (45/56)	85.7% (6/7)	85.7% (6/7)	90.3% (28/31)	57.1% (4/7)	25% (1/4)
sPTB at <37/40 wk	18% (56/319)	25.9% (7/27)	20.8% (7/34)	16.4% (31/189)	12.5% (7/56)	30.7% (4/13)
Progesterone	10.8% (15/138)	30.8% (4/13)	7.7% (1/13)	7.9% (6/76)	13.8% (4/29)	0% (0/6)

sPTB, spontaneous preterm birth.

Ridout et al. Preterm birth prediction by cervical length and quantitative fetal fibronectin in congenital uterine anomalies. Am J Obstet Gynecol 2019.

a consensus that short CL on TVUS correlates with increased risk of sPTB in women with CUA. However, these study reports do not comment on the differences between types of CUA. The studies are small (the largest comprising 120 women,[23] compared to 319 reported here) and therefore do not have sufficient power for this analysis. Increased sample size allowed our analysis to discern a difference in predictive tests, namely, qfFN and CL, between fusion and resorption defects, rather than examining the cohort as a single heterogeneous group.

Consistent with our findings, Airoldi et al highlighted no cervical shortening in the 2 women with didelphic uteri (n = 2/11) who went on to deliver preterm (n = 11).[20] The 2 studies describing CL measurement both extended their sampling windows up to 30 weeks[21] and 32 weeks,[23] respectively, and developed a new cutoff of 30 mm, based on their individual data set (n = 52).[21] With this increased sampling window, Crane et al reported 100% sensitivity for a CL cutoff of 30 mm. As these were only 3 of 3 events identified and both studies were sampling outside of current clinical guidelines, we believe that our data supersede this.

It is important to acknowledge the limitations of our study. Women and healthcare providers were not blinded to CL and qfFN assessments. The study population included women who were referred to preterm birth surveillance clinics for high-risk monitoring. We do not know the number of women with a uterine anomaly who were not referred for asymptomatic screening. Also, although this larger cohort allows us to draw some conclusions about individual subgroups, we recognize that we do not have adequate power to undertake further analysis investigating the additive value of qfFN and CL. Future research in women with resorption defects would help to elucidate the synergies between predictive tests, as well as seeking the ideal surveillance window and the CL and qfFN cutoffs for this population.

A further limitation was that women with septate uteri were a small group in this study. The data did not lend themselves to biological plausibility with regard to separating the groups into those who had had surgical removal of their septum and those who had not, and therefore we highlight this as an area that would benefit from future research. Arcuate uteri also appeared to be particularly high risk in our cohort; however, the numbers were small, and in this group all but 1 patient had additional risk factors. Therefore, CUA may have been an incidental finding, and a significant proportion of preterm deliveries may be due to etiology unrelated to CUA, for example, infection and inflammation.

If a short cervix (CL <25 mm) was detected within the surveillance period, an ultrasound-indicated cerclage may have been carried out, depending on local hospital clinical practice. Repeat analysis excluding women with intervention (cerclage and/or progesterone) confirmed that predictive markers were no better than chance in women with fusion defects, but that these markers do have clinical utility in women with resorption defects. The literature confirms the continued value of CL measurement as a reliable predictor of sPTB with cerclage in situ, and 80% of women who delivered preterm spontaneously did not develop a short CL during the surveillance period. Only 6% (18/319) of our total cohort had an ultrasound-indicated cerclage.

Conclusions and future research implications

Our findings suggest different etiological contributions to the pathophysiology of sPTB in CUA, which do not follow the predictable pattern of cervical shortening and dilatation seen in women who deliver early because of inflammation and infection. This needs to be accounted for when planning antenatal care, with potential implications for sPTB surveillance and intervention. ■

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