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# Accepted Manuscript



Cervical Length and Quantitative Fetal Fibronectin in the Prediction of Spontaneous Preterm Birth in Asymptomatic Women with Congenital Uterine Anomaly

Alexandra E. Ridout, L. Ibeto, Georgia Ross, J.R. Cook, L. Sykes, Anna L. David, Paul T. Seed, Rachel Tribe, Phillip R. Bennett, V. Terzidou, Andrew H. Shennan, Manju Chandiramani, Collaborators, R. Brown, S. Chatfield, Dana Sadeh

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1 **CERVICAL LENGTH AND QUANTITATIVE FETAL FIBRONECTIN IN THE**  
2 **PREDICTION OF SPONTANEOUS PRETERM BIRTH IN ASYMPTOMATIC**  
3 **WOMEN WITH CONGENITAL UTERINE ANOMALY**

4

5 Alexandra E Ridout<sup>1</sup>, L Ibeto<sup>2</sup>, Georgia Ross<sup>1</sup>, JR Cook<sup>2</sup>, L Sykes<sup>2</sup>, Anna L David<sup>3</sup>,  
6 Paul T Seed<sup>1</sup>, Rachel Tribe<sup>1</sup>, Phillip R Bennett<sup>2</sup>, V Terzidou<sup>2</sup>, Andrew H Shennan<sup>1</sup>,  
7 Manju Chandiramani<sup>1</sup>

8 Collaborators: R Brown<sup>2</sup>, S Chatfield<sup>2</sup>, Dana Sadeh<sup>3</sup>

9

10 <sup>1</sup>Womens Health Academic Centre, Kings College London, UK

11 <sup>2</sup>Parturition Research Group, Institute of Reproductive and Development Biology,  
12 Imperial College London, Du Cane Road, London W12 0NN, UK

13 <sup>3</sup>UCL EGA Institute for Women's Health, University College London, Medical School  
14 Building, 74 Huntley Street, London WC1E 6AU

15

16 Corresponding author: Dr Alexandra E Ridout

17 Email: [aeridout@gmail.com](mailto:aeridout@gmail.com)

18 Telephone: [0207 188 3639](tel:02071883639)

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27 **Condensation:** Predictive tests for preterm birth (cervical length and quantitative  
28 fetal fibronectin) do not have clinical utility in women with congenital uterine  
29 anomalies related to fusion defects.

30

31 **Short Title:** Preterm birth prediction by cervical length and quantitative fetal  
32 fibronectin in congenital uterine anomalies.

33

34 **AJOG at a GLANCE:**

35 **A: Why was the study conducted?**

- 36 • To assess the performance of current predictive markers of sPTB, quantitative  
37 fetal fibronectin (qfFN) and transvaginal cervical length (CL) measurement in  
38 asymptomatic high-risk women with Congenital Uterine Anomalies (CUA)
- 39 • To characterise rates of early delivery by type of CUA

40 **B: What are the key findings?**

- 41 • CUA, particularly fusion defects, are associated with high rates of late  
42 miscarriage and PTB
- 43 • CL and qfFN have utility in prediction of sPTB in women with resorption  
44 defects, however were no better than chance in women with fusion defects.  
45 This is contrary to other high-risk populations.”

46 **C: What does this study add to what is already known?**

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

50

51 **Key Words**

52 Bicornuate, Canalisation defects, Cervical length, Congenital uterine anomaly, Fetal  
53 fibronectin, Fusion defect, Unicornuate, Unification defects, Uterus didelphys,  
54 Preterm birth, Resorption defect

55

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ACCEPTED MANUSCRIPT

58 **Abstract**

59

60 **Background:** Congenital uterine anomalies (CUA) are associated with late  
61 miscarriage and spontaneous preterm birth (sPTB).

62

63 **Objectives:** Our aim was to 1) determine the rate of sPTB in each type of CUA and  
64 2) assess the performance of quantitative fetal fibronectin (qfFN) and transvaginal  
65 cervical length (CL) measurement by ultrasound in asymptomatic women with CUA  
66 for the prediction of sPTB at <34 and <37 weeks of gestation.

67

68 **Study design:** This was a retrospective cohort of women with CUA asymptomatic  
69 for sPTB, from four UK tertiary referral centres (2001-2016). CUAs were categorised  
70 into fusion (unicornuate, didelphic and bicornuate uteri) or resorption defects  
71 (septate, with or without resection and arcuate uteri), based on pre-pregnancy  
72 diagnosis.

73 All women underwent serial transvaginal ultrasound CL assessment in the second  
74 trimester (16 to 24 weeks' gestation); a subgroup underwent qfFN testing from 18  
75 weeks' gestation. We investigated the relationship between CUA and predictive test  
76 performance for sPTB before 34 and 37 weeks' gestation.

77

78 **Results:** Three hundred and nineteen women were identified as having CUA within  
79 our high-risk population. 7% (23/319) delivered spontaneously <34 weeks, and 18%  
80 (56/319) <37 weeks' gestation. Rates of sPTB by type were: 26% (7/27) for

81 unicornuate, 21% (7/34) for didelphic, 16% (31/189) for bicornuate, 13% (7/56) for  
82 septate and 31% (4/13) for arcuate.

83 80% (45/56) of women who had sPTB <37 weeks did not develop a short CL (<25  
84 mm) during the surveillance period (16-24 weeks). The diagnostic accuracy of short  
85 CL had low sensitivity (20.3) for predicting sPTB <34 weeks.

86 **Cervical Length** had ROC AUC of 0.56 (95% CI 0.48 to 0.64) and 0.59 (95% CI  
87 0.55 to 0.64) for prediction of sPTB <34 and 37 weeks' respectively.

88 The AUC for CL to predict sPTB <34 weeks was 0.48 for fusion defects (95% CI 0.39  
89 to 0.57) but 0.78 (95% CI 0.66 to 0.91) for women with resorption defects.

90 Overall **quantitative fetal fibronectin** had a AUC of 0.63 (95% CI 0.49 to 0.77) and  
91 0.58 (95% CI 0.49 to 0.68) for prediction of sPTB <34 and 37 weeks, respectively.

92 AUC for prediction of sPTB <37 weeks with qfFN for fusion defects was 0.52 (95%  
93 CI 0.41 to 0.63), but 0.79 (0.63 to 0.95) for women with resorption defects. Results  
94 were similar when women with intervention were excluded.

95

96 **Conclusion:** Commonly used markers CL and qfFN have utility in prediction of  
97 sPTB in resorption congenital uterine defects but not in fusion defects. This is  
98 contrary to other high-risk populations. These findings need to be accounted for  
99 when planning antenatal care and have potential implications for predictive tests  
100 used in sPTB surveillance and intervention.

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105

**106 Background**

107 The presence of a congenital uterine anomaly (CUA) is a well-established cause of  
108 pregnancy complications, including infertility, recurrent first and second trimester  
109 miscarriages, preterm birth (PTB) with or without preterm pre-labour rupture of  
110 membranes (PPROM), as well as intra-uterine growth restriction, fetal malposition  
111 and caesarean section<sup>1-4</sup>. The types of CUA are individually associated with varying  
112 degrees of adverse outcomes.

113

114 Formation of the female reproductive tract involves a chain of complex steps, with  
115 differentiation, migration, unification and subsequent canalization of the Müllerian  
116 ducts<sup>5</sup>. A deviation anywhere along this stepwise development pathway will result in  
117 a CUA, from arcuate uterus, a subtle variation from normal anatomy, to complete  
118 failure of fusion of the Müllerian ducts, with two discrete cervical canals and uterine  
119 cavities (uterus didelphys). Recognition of CUA is often only noted in the presence of  
120 pathology, e.g. recurrent miscarriage or early delivery. However, in women with  
121 recurrent pregnancy loss, the rate can be as high as 10%<sup>6,7</sup>.

122

123 While specific CUAs differ in rates of sPTB, and reliable control data to quantify this  
124 is lacking, all are associated with poor reproductive outcomes<sup>2</sup>, emphasizing the  
125 clinical importance of antenatal surveillance for this group. Identifying those most at  
126 risk of sPTB is the strategy currently employed globally. The value of quantitative  
127 fFN and CL has been proven in large prospective cohorts however reports have  
128 concentrated on asymptomatic singletons with prior preterm birth, late miscarriage or



129 cervical surgery. There is limited evidence to support the use of predictive markers in  
130 women with CUAs.

131

132 We prospectively collected serial CL and qfFN data from a large cohort of high-risk  
133 women with congenital uterine anomalies who were asymptomatic for sPTB. Our aim  
134 was to determine the clinical utility of current used predictive markers of sPTB in this  
135 group.

136

### 137 **Study Design**

138 This is a retrospective cohort study of prospectively collected data from  
139 asymptomatic pregnant women with CUAs presenting to high-risk preterm  
140 surveillance clinics (PSC) at four tertiary referral hospitals in London (Queen  
141 Charlotte's and Chelsea Hospital, St Thomas' Hospital, Chelsea and Westminster  
142 Hospital and University College London Hospital), over a fifteen-year period (2001 to  
143 2016). Women were included if the diagnosis of a CUA (unicornuate, didelphic,  
144 bicornuate, septate or arcuate) was made prior to pregnancy by imaging or surgery,  
145 and classified according to the American Fertility Society classification (AFS) (1988)  
146 (currently the American Society of Reproductive Medicine). Surgical repair was  
147 recorded, as were any additional referral risk factors (one or more previous sPTB or  
148 PPRM), previous late miscarriage (14 to 23<sup>+6</sup> weeks) or previous cervical surgery).

149

150 As part of routine clinical care within the preterm surveillance clinics, women  
151 underwent serial transvaginal ultrasound (TVUS) surveillance of CL between 16 and  
152 24 weeks' (second trimester screening). Frequency of surveillance (TV USS and  
153 qfFN) varied between 2 and 4 weeks according to clinical need and continued until

154 24weeks, independent of prophylactic intervention (cerclage and/or progesterone).  
155 Elective cervical cerclage was offered as per contemporaneous clinical practice  
156 based on the woman's previous obstetric history or ultrasound indicated cerclage  
157 based on a short CL in the index pregnancy, defined as a CL <25 mm <24 weeks'  
158 gestation. In a subgroup of women, qfFN measurement was carried out at each visit  
159 just prior to ultrasound, between 18 and 24 weeks of gestation. FFN samples from  
160 women who reported sexual intercourse within 24 hours or with frank bleeding were  
161 excluded from the analysis according to manufacturer's instructions (Hologic Inc,  
162 USA).

163  
164 Maternal demographic data, serial CL and qfFN measurements, and maternal and  
165 neonatal outcome details were analysed. Women were considered to have had a  
166 spontaneous preterm birth if they had spontaneous onset of labour, or experienced  
167 preterm rupture of membranes and delivered prematurely, regardless of mode of  
168 delivery. Women with iatrogenic delivery before the gestational time point of interest,  
169 twin pregnancies, and those with incomplete outcome data were excluded from the  
170 analysis. We repeated the analysis excluding women with intervention in situ.

171  
172 This study was exempt from requiring ethical approval under the UK Health and  
173 Social Care Act 2012, which states that research involving anonymised routinely  
174 collected clinical data is excluded from research ethics committee review.

175

#### 176 Technique of qfFN measurement

177 During speculum examination, a polyester swab was inserted into the posterior fornix  
178 of the vagina (10 seconds) to collect a sample of cervicovaginal fluid. The swab was

179 placed into the test buffer solution and analyzed immediately. An aliquot (200  
180 microliters) of the sample was analyzed using the quantitative Rapid fFN 10Q  
181 analyzer according to manufacturer' s instructions. All clinicians received appropriate  
182 training to use the analyzers.

183

184 Thresholds of 10 (lower limit of test), 50 (previous standard), and 200 ng/mL (based  
185 on existing literature) were predefined. Quantitative fFN assay results are reported in  
186 units of ng/mL and the result was standardized using purified fetal fibronectin and  
187 A128 measurement with an extinction coefficient = 1.28. The reliability of the Rapid  
188 10Q analyzer has previously been reported. For the 10Q Assay the intra-assay CV is  
189 5.7% - 7.3% and the intra-assay CV is 5.9% - 7.5%. Experiments that were  
190 performed during product development confirmed a good correlation  
191 between ELISA and 10Q tests (slope = 0.97;  $r^2 = 0.82$ ) [Personal communication  
192 with Jerome Lapointe, Hologic].

193

#### 194 Technique of cervical length assessment

195 Serial CL assessment was undertaken in accordance with standardized guidelines  
196 by trained operators.<sup>11,12</sup> In summary, the woman was asked to empty her bladder  
197 and then the TVUS probe was inserted into the anterior fornix of the vagina to obtain  
198 a sagittal long axis view of the echogenic endocervical mucosa along the length of  
199 the cervical canal, allowing identification of both the internal and external os. Without  
200 causing undue pressure on the cervix with the probe to avoid falsely elongating it,  
201 the linear distance between the external and internal os was recorded three times in  
202 millimeters over a minimum of three minutes using optimal magnification and zoom  
203 settings and the shortest CL was recorded. Transfundal pressure was exerted for 15

204 seconds and subsequent demonstration of a cervical funnel was noted if present.  
205 The shortest total closed CL of three measurements was considered the length for  
206 analysis, with “short” CL defined as less than 25mm.

207

### 208 Statistical analysis

209 Descriptive statistics were used to depict the study population. Predictive statistics  
210 were carried out to determine if predictive tests (CL and qfFN) accurately predicted  
211 sPTB <34 and 37weeks' gestation. Statistical analysis was performed using Stata  
212 14.0. Receiver operating characteristic (ROC) curves were generated and  
213 compared. Data from repeated sampling of the same individuals was analysed.  
214 Therefore clustered bootstrapping with bias correction was used to calculate  
215 confidence intervals for ROC curves (Ng, Grieve & Carpenter, 2013)<sup>13</sup>. Quantitative  
216 fFN analysis was carried out for a subgroup of women. Due to sample size,  
217 descriptive data alone were generated for this group.

218

### 219 Results

220 Four hundred and twenty-nine women with congenital uterine anomalies were  
221 identified in the four high-risk preterm surveillance clinics. One hundred and ten  
222 women were subsequently excluded from analysis as a result of missing outcome  
223 data/uterine anomaly classification (n=91), multiple pregnancy (n=9) and incomplete  
224 qfFN or CL data (n=10).

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

229 with septate and 31% (4/13) with arcuate uteri. Overall, the sPTB rate was 7%  
230 (23/319) at <34 weeks and 18% (56/319) at <37 weeks' gestation.

231 Two hundred and fifty-seven women (81%, 257/319) had CUA as their sole risk  
232 factor (ie. no additional history of sPTB/late miscarriage or cervical surgery). Rates of  
233 sPTB <37 weeks for this group were as follows: 27% (7/26) for unicornuate, 20%  
234 (6/30) for didelphic, 9% (13/143) for bicornuate, 13% (6/48) for septate and 10%  
235 (1/10) for women with an arcuate uterus (Table 1).

236 Women with septate uteri had a high rate of previous 1<sup>st</sup> trimester miscarriage (42%,  
237 15/36). One fifth (21%, 36/173) of women with bicornuate uteri had a previous  
238 history of sPTB. Over 20% (2/9) of the cohort with arcuate uteri had a history of  $\geq 1$   
239 previous late miscarriage. Maternal characteristics relevant to risk of sPTB are  
240 shown in Table 2.

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

244

#### 245 **Cervical length assessment**

246 Three hundred and nineteen women received a total of 955 TVUSS CL  
247 measurements. On average, each women had 2.2 measurements per pregnancy  
248 (range 1 to 6). Twenty-nine women in this high-risk population (9%) were found to  
249 have a short CL (<25 mm), of whom 48% (14/29) delivered <37 weeks.

250 CL was a poor predictor of sPTB <34 and 37 weeks' gestation when the cohort was  
251 analysed as a whole (AUC 0.56 (95% CI 0.48 to 0.64) and 0.59 (95% CI 0.55 to

252 0.64) respectively) (Table 3), with a low diagnostic sensitivity when a cutoff of <25  
253 mm was used (20.3 and 15.2 for sPTB < 34 and 37 weeks' respectively).

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

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

262 Prediction of sPTB at <34 and 37 weeks was poor in women with fusion defects  
263 (AUC 0.48 (95% CI 0.39 to 0.57) and AUC 0.60 (95% CI 0.55 to 0.65). Figure 1. For  
264 specific fusion defects, CL was also not predictive of sPTB <37 weeks (unicornuate  
265 0.48 (95% CI 0.34 to 0.62), didelphic 0.55 (95% CI 0.42 to 0.68) and 0.62 (95% CI  
266 0.56 to 0.69) for bicornuate uteri). Diagnostic accuracy for individual CUA defects  
267 can be seen in Table 4.

268 Results were similar after excluding women with intervention (cerclage and/or  
269 progesterone) [unicornuate 0.55 (95% 0.39 to 0.74, didelphic 0.55, 95% CI 0.34 to  
270 0.70 and 0.62 (95% CI 0.51 to 0.72) for bicornuate uteri].

271

272 **Quantitative fetal fibronectin**

273 One hundred and fifty five women underwent 793 cervicovaginal qfFN protein  
274 analysis. Overall qfFN had a ROC AUC of 0.63 (95% CI 0.49 to 0.77) and 0.58 (95%  
275 CI 0.49 to 0.68) for prediction of sPTB <34 and 37 weeks, respectively.

276 We found qfFN to be an accurate test of sPTB <34 and 37 weeks in women with  
277 resorption defects (AUC 0.83 (95% CI 0.62 to 1.00) and AUC 0.79 (95% CI 0.63 to  
278 0.95) respectively) (Figure 3). This did not hold true for fusion defects (AUC for sPTB  
279 <37 weeks 0.52 (95% CI 0.41 to 0.63)).

## 280 **Management**

281 Over half of the women in our cohort delivered by caesarean section (56%,  
282 124/221), with the highest number in those with didelphic (77%, 17/22) and  
283 unicornuate uteri (73%, 16/22). Sixty per cent (9/15) of women with uterus didelphys  
284 had a fetal malposition at time of delivery (Table 5). In total, 11% (35/319) of women  
285 had a cervical cerclage during their pregnancy. 51% (18/35) were ultrasound  
286 indicated, based on a CL <25mm at gestation <24 weeks. 11% of women were  
287 prescribed progesterone during their pregnancy, although we only have data on  
288 progesterone prescribing practices for 138/319 women (Table 6). 80% (45/56) of  
289 women who delivered spontaneously <37 weeks' did not develop a short CL during  
290 our surveillance period (16 to 24 weeks').

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298 **Comment**

299

300 **Principle Findings:**

301 Commonly used markers, CL and qfFN, have utility in prediction of sPTB in  
302 resorption congenital uterine defects but not in fusion defects. This is contrary to  
303 other high-risk populations. 80% (45/56) of women who went into spontaneous  
304 labour preterm did not develop a short CL during the antenatal surveillance period.

305

306 In our cohort, 21% (7/34) women with a didelphic uterus (a fusion defect) delivered  
307 <37 weeks' gestation, and 8% (3/34) <34 weeks' gestation. Early pregnancy CL  
308 measurement was no better than chance at predicting delivery <37 weeks, with poor  
309 AUC, sensitivity and negative predictive value.

310

311 Asymptomatic qfFN screening in our whole cohort was a poor predictor of delivery at  
312 <34 weeks' gestation. This was confirmed for fusion defects (<34 weeks AUC 0.55,  
313 95% CI 0.39 to 0.70, <37 weeks AUC 0.52, 95% CI 0.41 to 0.63). This is contrary to  
314 other cohorts at high risk of sPTB (e.g. history of late miscarriage) and therefore it is  
315 important that clinicians are aware of this when planning antenatal surveillance and  
316 choosing predictive tests for sPTB.

317

318 **Clinical Implications:**



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

328

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

338

339 The difference in predictive test performance between fusion and resorption groups  
340 may be related to the underlying mechanism of preterm birth. In women with  
341 resorption defects (septate and arcuate uterus), predictive markers performed as  
342 seen in other high-risk populations; both CL and qfFN were useful predictors of sPTB

343 <34 and 37 weeks' gestation. Resorption defects have relatively normal uterine  
344 architecture. By definition an arcuate uterus has an intrauterine indentation of less  
345 than 1cm and therefore it is plausible that it does not impact on either the cause of  
346 preterm delivery or the mechanism by which markers CL and qfFN predict delivery.

347

348 For more severe structural anomalies, such as unicornuate or uterus didelphys, the  
349 converse is likely to be true, and poor pregnancy outcome is hypothesized to be  
350 related to stretch effects secondary to altered uterine architecture, decreased muscle  
351 mass and abnormal cervical architecture, with or without abnormal uterine  
352 vasculature<sup>18</sup>. If the cervix plays no part in the aetiology of labour onset, it may not  
353 predict delivery in this group. Further research needs to focus on novel predictive  
354 markers in this high-risk group.

355

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

365

366 **Strengths and Weaknesses:**

367 Three previous studies reported the use of CL measurement in women with CUA<sup>20–</sup>  
368 <sup>22</sup>, and one has evaluated the addition of qualitative fFN<sup>23</sup>. Consensus concluded  
369 that short CL on TVUS correlates with increased risk of sPTB in women with CUA.  
370 However these studies do not comment on the differences between types of CUA.  
371 They are small (the largest 120 women<sup>23</sup> compared to 319 reported here) and  
372 therefore do not have sufficient power for this analysis. Increased sample size  
373 allowed our analysis to discern a difference in predictive tests, qfFN and CL,  
374 between fusion and resorption defects, rather than examining the cohort as one  
375 heterogeneous group.

376

377 Consistent with our findings, Airoidi et al (2005) highlighted no cervical shortening in  
378 the two women with didelphic uteri (n=2/11) who went on to deliver preterm (n=11)<sup>20</sup>.  
379 The two studies describing CL measurement both extended their sampling windows  
380 up to 30<sup>21</sup> and 32<sup>23</sup> weeks respectively, and developed a new cut off of 30mm,  
381 based on their individual data set (n=52)<sup>21</sup>. With this increased sampling window  
382 Crane et al report 100% sensitivity for a CL cut off of 30mm. As this was only 3 out of  
383 3 events identified and both studies were sampling outside of current clinical  
384 guidelines, we believe our data supersedes this.

385

386 It is important to acknowledge the limitations of our study. Women and healthcare  
387 providers were not blinded to CL and qfFN assessments. The study population  
388 included women who were referred to a preterm birth surveillance clinics for high-risk  
389 monitoring. We do not know the number of women with a uterine anomaly who were  
390 not referred for asymptomatic screening. Also while this larger cohort allows us to

391 draw some conclusions about individual subgroups, we recognise we do not have  
392 adequate power to undertake further analysis investigating the additive value of qfFN  
393 and CL. Future research in women with resorption defects would help understand  
394 the synergies between predictive tests, as well as seeking the ideal surveillance  
395 window and CL and qfFN cut offs for this population.

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

406

407 If a short cervix (CL <25mm) was detected within the surveillance period, an  
408 ultrasound-indicated cerclage may have been carried out, depending on local  
409 hospital clinical practice. Repeat analysis excluding women with intervention  
410 (cerclage and/or progesterone) confirmed predictive markers were no better than  
411 chance in women with fusion defects but have clinical utility in women with resorption  
412 defects. The literature confirms the continued value of CL measurement as a reliable  
413 predictor of sPTB with cerclage in situ, and 80% of women who delivered preterm  
414 spontaneous did not develop a short CL during the surveillance period. Only 6%  
415 (18/319) of our total cohort had an ultrasound-indicated cerclage.

416

417 **Conclusions and future research implications**

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

423

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528 **Table 1: Pregnancy outcome in women with congenital uterine anomaly**

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

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551 **Table 2: Maternal Characteristics of women with congenital uterine anomaly**

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

552 Results given as % (n) or median [interquartile range]

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560 **Table 3: Accuracy of qfFN and CL for the prediction of sPTB**

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Type of anomaly	CL prediction		qfFN prediction	
	ROC AUC		ROC AUC	
	95% confidence intervals		95% confidence intervals	
<b>Whole cohort (n=319)</b>				
<i>sPTB&lt;34weeks</i>	0.56	0.48 to 0.64	0.63	0.49 to 0.77
<i>sPTB&lt;37weeks</i>	0.59	0.55 to 0.64	0.58	0.49 to 0.68
<b>Fusion defects</b>				
<i>sPTB&lt;34weeks</i>	0.48	0.39 to 0.57	0.55	0.39 to 0.70
<i>sPTB&lt;37weeks</i>	0.60	0.55 to 0.65	0.52	0.41 to 0.63
<b>Resorption defects</b>				
<i>sPTB&lt;34weeks</i>	0.78	0.66 to 0.91	0.83	0.62 to 1.00
<i>sPTB&lt;37weeks</i>	0.66	0.55 to 0.78	0.79	0.63 to 0.95

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580 **Table 4: Accuracy of CL for the prediction of sPTB in subgroups**

Type of anomaly	ROC AUC	
	95% confidence intervals	
<b>Unicornuate (n=27)</b>		
<i>sPTB&lt;34weeks</i>	0.56	0.32 to 0.80
<i>sPTB&lt;37weeks</i>	0.48	0.34 to 0.62
<b>Didelphys (n=34)</b>		
<i>sPTB&lt;34weeks</i>	0.50	0.31 to 0.70
<i>sPTB&lt;37weeks</i>	0.55	0.42 to 0.68
<b>Bicornuate (n=189)</b>		
<i>sPTB&lt;34weeks</i>	0.46	0.35 to 0.56
<i>sPTB&lt;37weeks</i>	0.62	0.56 to 0.69
<b>Septate (n=56)</b>		
<i>sPTB&lt;34weeks</i>	0.80	0.62 to 0.97
<i>sPTB&lt;37weeks</i>	0.61	0.47 to 0.76
<b>Arcuate (n=13)</b>		
<i>sPTB&lt;34weeks</i>	0.79	0.51 to 0.98
<i>sPTB&lt;37weeks</i>	0.79	0.51 to 0.98

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595 **Table 5: Pregnancy outcome in women with congenital uterine anomaly**

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

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614 **Table 6: Antenatal management in asymptomatic women with CUA**

<b>Pregnancy Outcome</b>	<b>Cohort (n=319)</b>	<b>Unicornuate (n=27)</b>	<b>Didelphys (n=34)</b>	<b>Bicornuate (n=189)</b>	<b>Septate (n=56)</b>	<b>Arcuate (n=13)</b>
<b>Cerclage</b>	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)
<i>sPTB &lt;37/40</i>	23.5% (5/18)	0% (0/2)	50% (1/2)	(5/11)	50% (1/2)	100% (1/1)
<i>sPTB &lt;34/40</i>	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)
<i>sPTB &lt;37/40</i>	23.5% (4/17)	0% (0/1)	33.3% (1/3)	25% (2/8)	20% (1/5)	0% (0/13)
<i>sPTB &lt;34/40</i>	17.6% (3/17)	0% (0/1)	33.3% (1/3)	12.5% (1/8)	20% (1/5)	0% (0/13)
<b>sPTB without short CL</b>	80.4% (45/56)	85.7% (6/7)	85.7% (6/7)	90.3% (28/31)	57.1% (4/7)	25% (1/4)
<i>sPTB &lt;37/40</i>	18% (56/319)	25.9% (7/27)	20.8% (7/34)	16.4% (31/189)	12.5% (7/56)	30.7% (4/13)
<b>Progesterone</b>	10.8% (15/138)	30.8% (4/13)	7.7% (1/13)	7.9% (6/76)	13.8% (4/29)	0% (0/6)

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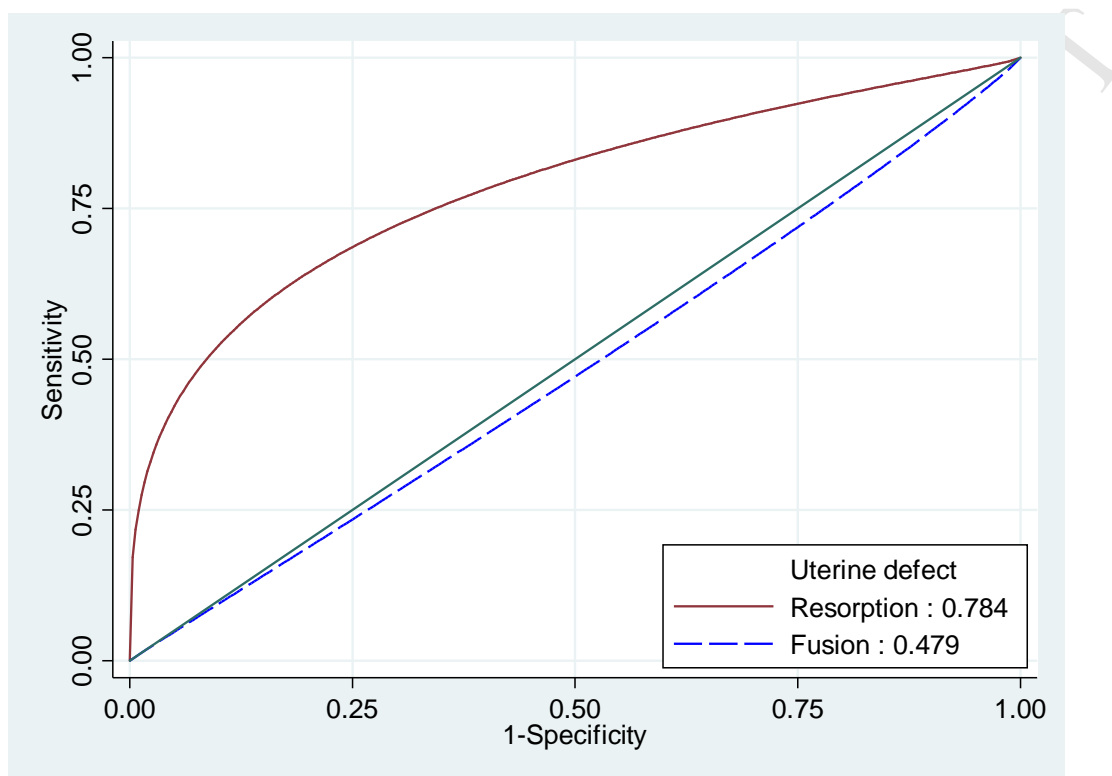
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624 **Figure 1: TVUSS CL to predict sPTB <34weeks in CUA grouped by fusion or**625 **resorption defect**

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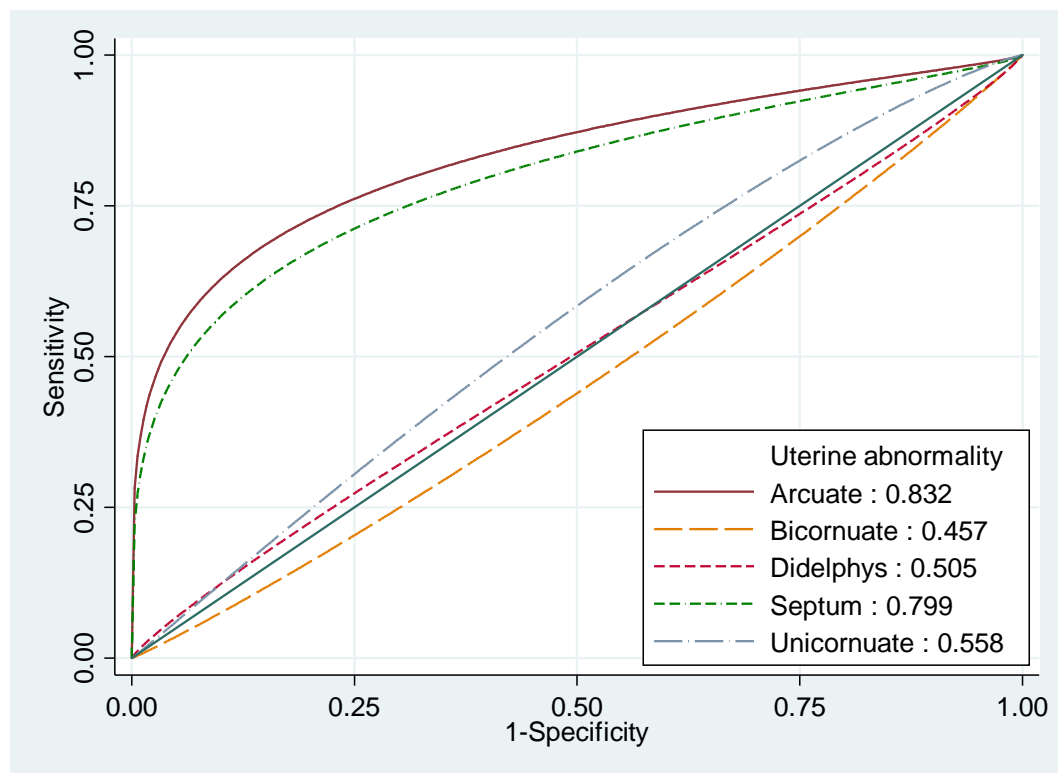
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635 **Figure 2: TVUSS CL to predict sPTB <34 weeks by type of CUA defect**

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637 *\*using binomial modeling*

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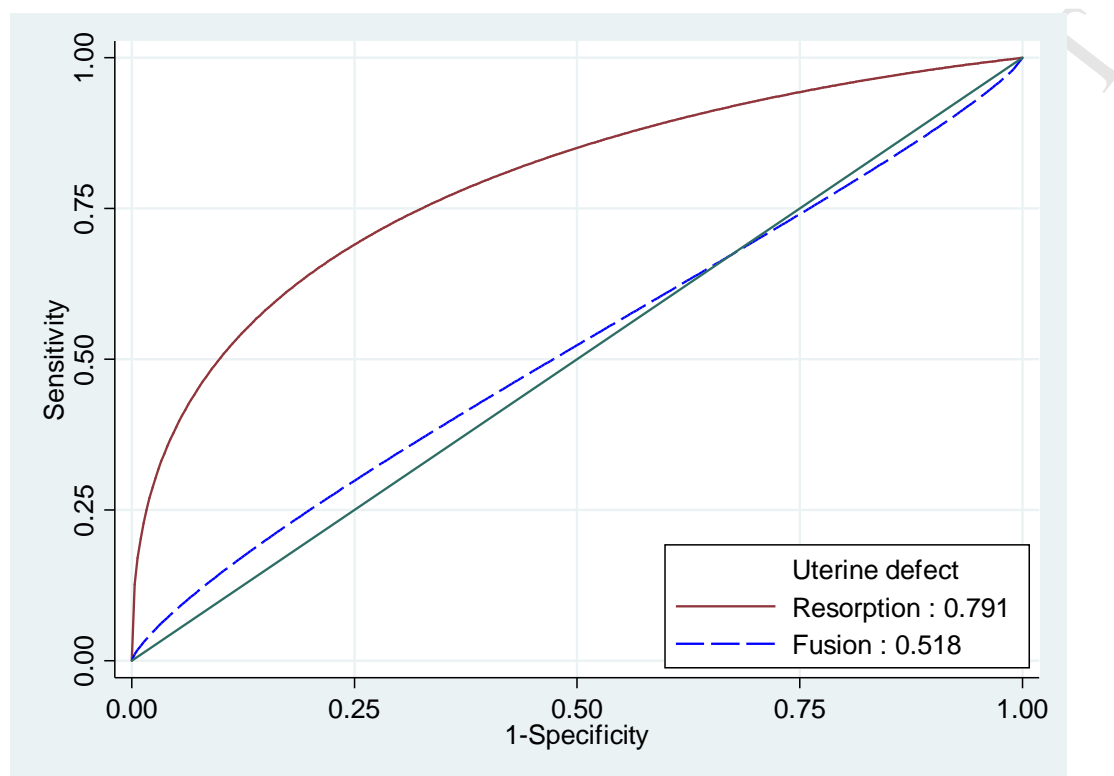
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646 **Figure 3: Quantitative fetal fibronectin to predict sPTB <37 weeks grouped by**647 **fusion or resorption defect**

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**Table 1: Pregnancy outcome in women with congenital uterine anomaly**

Pregnancy Outcome	Cohort (n=319)	Unicornuate (n=27)	Didelphys (n=34)	Bicornuate (n=189)	Septate (n=56)	Arcuate (n=13)
sPTB <37 weeks	17.6% (56)	25.9% (7)	20.6% (7)	16.4% (31)	12.5% (7)	30.8% (4)
sPTB < 34 weeks	7.2% (23)	3.7% (1)	8.8% (3)	6.3% (12)	5.4% (3)	30.8% (4)
sPTB < 37 weeks when CUA 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)

**Table 2: Maternal Characteristics of women with congenital uterine anomaly**

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

Table 3: Accuracy of qfFN and CL for the prediction of sPTB

Type of anomaly	CL prediction		qfFN prediction	
	ROC AUC		ROC AUC	
	95% confidence intervals		95% confidence intervals	
<b>Whole cohort (n=319)</b>				
<i>sPTB&lt;34weeks</i>	0.56	0.48 to 0.64	0.63	0.49 to 0.77
<i>sPTB&lt;37weeks</i>	0.59	0.55 to 0.64	0.58	0.49 to 0.68
<b>Fusion defects</b>				
<i>sPTB&lt;34weeks</i>	0.48	0.39 to 0.57	0.55	0.39 to 0.70
<i>sPTB&lt;37weeks</i>	0.60	0.55 to 0.65	0.52	0.41 to 0.63
<b>Resorption defects</b>				
<i>sPTB&lt;34weeks</i>	0.78	0.66 to 0.91	0.83	0.62 to 1.00
<i>sPTB&lt;37weeks</i>	0.66	0.55 to 0.78	0.79	0.63 to 0.95

**Table 4: Accuracy of CL for the prediction of sPTB in subgroups**

Type of anomaly	ROC AUC	
	95% confidence intervals	
<b>Unicornuate (n=27)</b>		
<i>sPTB&lt;34weeks</i>	0.56	0.32 to 0.80
<i>sPTB&lt;37weeks</i>	0.48	0.34 to 0.62
<b>Didelphys (n=34)</b>		
<i>sPTB&lt;34weeks</i>	0.50	0.31 to 0.70
<i>sPTB&lt;37weeks</i>	0.55	0.42 to 0.68
<b>Bicornuate (n=189)</b>		
<i>sPTB&lt;34weeks</i>	0.46	0.35 to 0.56
<i>sPTB&lt;37weeks</i>	0.62	0.56 to 0.69
<b>Septate (n=56)</b>		
<i>sPTB&lt;34weeks</i>	0.80	0.62 to 0.97
<i>sPTB&lt;37weeks</i>	0.61	0.47 to 0.76
<b>Arcuate (n=13)</b>		
<i>sPTB&lt;34weeks</i>	0.79	0.51 to 0.98
<i>sPTB&lt;37weeks</i>	0.79	0.51 to 0.98

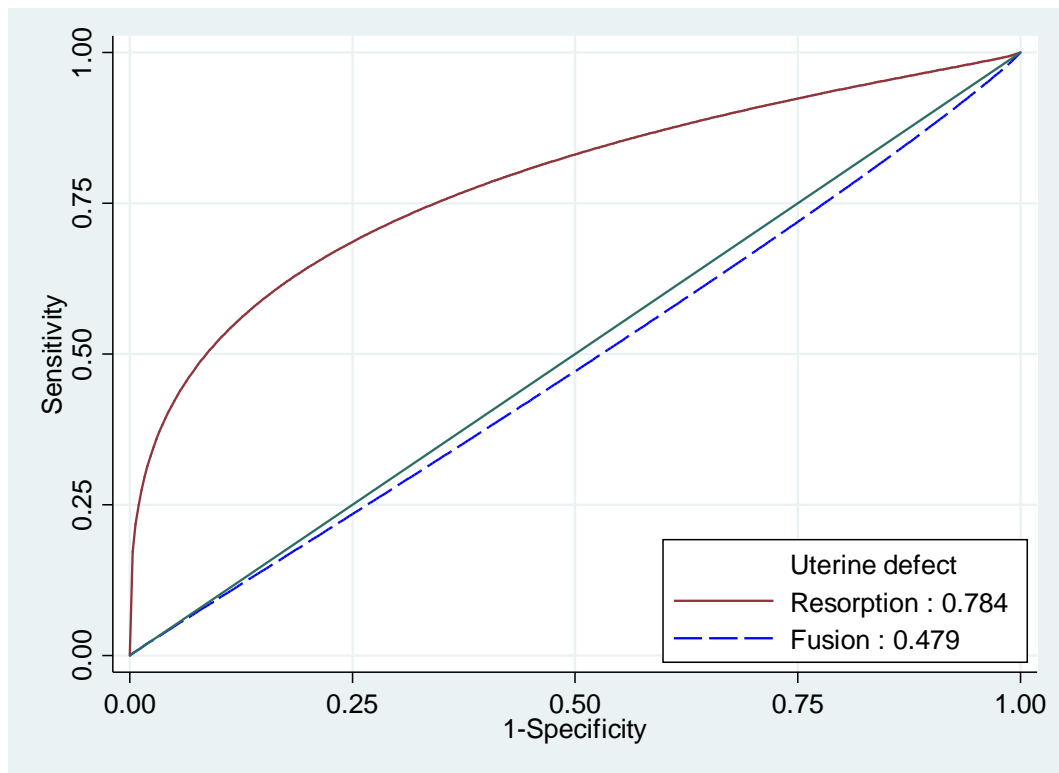
**Table 5: Pregnancy outcome in women with congenital uterine anomaly**

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

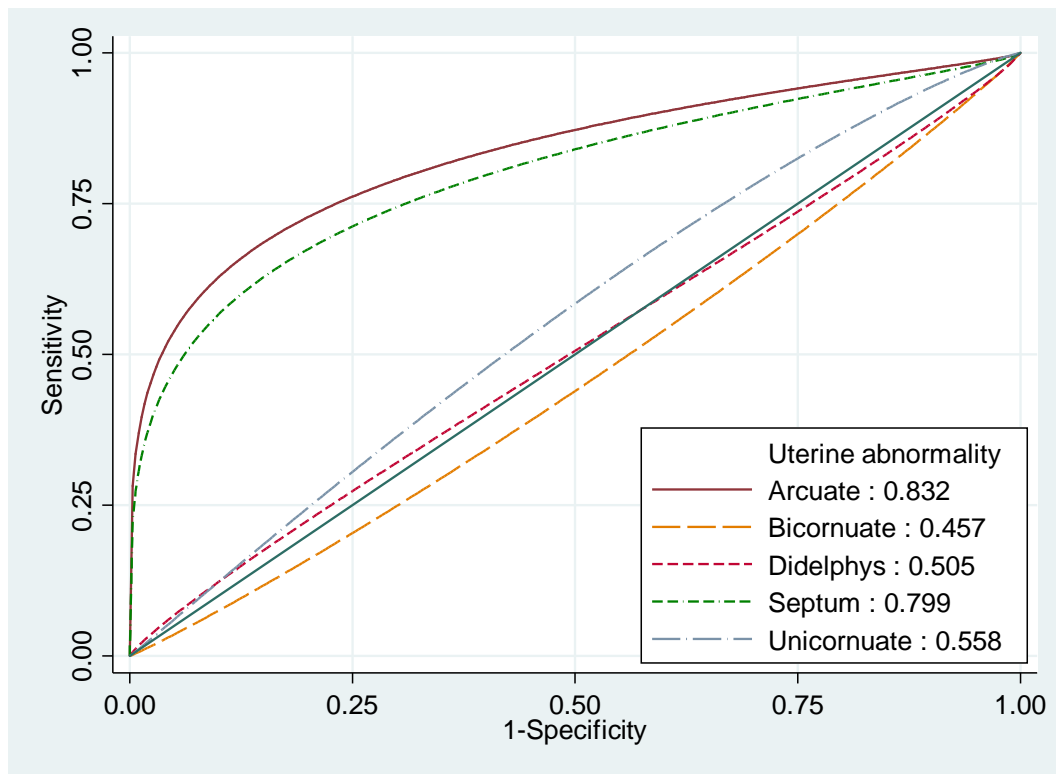
Table 6: Antenatal management in asymptomatic women with CUA

Pregnancy Outcome	Cohort (n=319)	Unicornuate (n=27)	Didelphys (n=34)	Bicornuate (n=189)	Septate (n=56)	Arcuate (n=13)
<b>Cerclage</b>	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 <37/40	23.5% (5/18)	0% (0/2)	50% (1/2)	(5/11)	50% (1/2)	100% (1/1)
sPTB <34/40	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 <37/40	23.5% (4/17)	0% (0/1)	33.3% (1/3)	25% (2/8)	20% (1/5)	0% (0/13)
sPTB <34/40	17.6% (3/17)	0% (0/1)	33.3% (1/3)	12.5% (1/8)	20% (1/5)	0% (0/13)
<b>sPTB without short CL</b>	80.4% (45/56)	85.7% (6/7)	85.7% (6/7)	90.3% (28/31)	57.1% (4/7)	25% (1/4)
sPTB <37/40	18% (56/319)	25.9% (7/27)	20.8% (7/34)	16.4% (31/189)	12.5% (7/56)	30.7% (4/13)
<b>Progesterone</b>	10.8% (15/138)	30.8% (4/13)	7.7% (1/13)	7.9% (6/76)	13.8% (4/29)	0% (0/6)

Figure 1: TVUSS CL to predict sPTB <34weeks in CUA grouped by fusion or resorption defect





**Figure 2: TVUSS CL to predict sPTB <34 weeks by type of CUA defect**

*\*using binomial modeling*

**Figure 3: Quantitative fetal fibronectin to predict sPTB <37 weeks grouped by fusion or resorption defect**

