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ORIGINAL ARTICLE

Risk of spontaneous preterm birth in IVF-conceived twin pregnancies

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ABSTRACT

Objective: To compare the mean transvaginal ultrasound (TVU) cervical length (CL) at midtrimester in screening for preterm birth in *in vitro* (IVF)-conceived twin pregnancies versus spontaneously-conceived twin pregnancies.

Methods: This was a retrospective cohort study. Potential study subjects were identified at the time of a routine second trimester fetal ultrasound exam at 18 0/7 to 23 6/7-week gestation. All women with twin diamniotic pregnancies screened with a single TVU CL for this trial were included. Mean TVU CLs were compared between IVF-conceived twin pregnancies and spontaneously-conceived twin pregnancies. The relationship of TVU CL with gestational age at delivery was assessed. Incidence of short TVU CL, defined as TVU CL $\leq$30 mm, was also calculated in the two groups. The primary outcome was the mean of TVU CL. Distribution of CL was determined and normality was examined in both groups

Results: A total of 668 women with diamniotic twin pregnancies who underwent TVU CL screening between 18 0/6 and 23 6/7 weeks were included. 158 (23.7%) were IVF-conceived pregnancies, and 510 (76.3%) were spontaneously-conceived pregnancies. No women received progesterone, pessary, or cerclage for preterm birth prevention during pregnancy. The mean TVU CL was significantly lower in the IVF-conceived group (32.2 ± 10.5 mm) compared to the spontaneously-conceived group (34.1 ± 9.1 mm) (mean difference (MD) − 1.90 mm, 95%CI −3.72 to −0.08). The incidence of TVU CL $\leq$30 mm was 30.4% in the IVF-conceived group and 21.6% in the spontaneously-conceived group (adjusted odds ratio (aOR) 1.59, 95%CI 1.06–2.37). IVF-conceived twins had a significantly higher risk of spontaneous preterm birth <34 weeks (32.9 versus 21.2%; aOR 1.83, 95% confidence interval (CI) 1.23–2.71) and higher rate of delivery due to spontaneous onset of labor (64.5 versus 54.9%; aOR 1.50, 95%CI 1.03–2.17). For any given TVU CL measured between 18 0–7 and 23 6/7 weeks, gestational age at delivery for IVF-conceived twins was earlier by about 1 week on average compared with spontaneously-conceived twins.

Conclusions: The higher rate of spontaneous preterm birth in IVF-conceived twin pregnancies is predicted by lower midtrimester TVU CL, as well as by the lower gestational age at birth per any given CL in the IVF-conceived compared to the spontaneously-conceived twin pregnancies.

Introduction

Preterm birth (PTB) is a leading cause of perinatal morbidity and mortality [1]. Over the last few years, cervical assessment has moved from digital examination to ultrasound evaluation, and ultrasound of the cervix has been the focus of much research [2–6]. Transvaginal ultrasound (TVU) cervical length (CL) has been assessed in several populations (e.g. asymptomatic women as well as women with symptoms of preterm labor or premature rupture of membranes) [4] to evaluate the risk of spontaneous PTB (SPTB) [7], in women before induction of labor to predict induction outcome [8], and at term in predicting the onset of spontaneous labor with moderate degree of accuracy [9]. A short TVU CL has been shown to be a good predictor of SPTB in both singletons and twins [4]; and has been shown to be more accurate than digital examination or fetal fibronectin in predicting SPTB [4,7,10].

Multifetal gestations are at increased risk of both SPTB and indicated PTB [1]. For example, the rate of PTB at <34 and <32 weeks in twin pregnancies has been shown to be 17% and 9%, compared with about 2% and 1% in singleton gestations, respectively [1]. Over the past decades, the incidence of twin pregnancies in the USA has increased, reaching a new high of 33.7 per 1000 total births in 2015 [1,11]. The rise in

multiple birth rates has been associated with expanded use of fertility therapies, and assisted reproductive technology (ART), including *in vitro* fertilization (IVF), and older maternal age at childbearing [1,11]. The percentage of multiple-birth infants in the USA that are IVF-conceived is about 40% [11]. IVF-conceived twin pregnancies have different complication rates, including higher risk of cesarean delivery, intrauterine growth restriction, preeclampsia, congenital malformations, low birth weight, and higher risk of PTB, compared to spontaneously-conceived twin pregnancies [12]. Although the higher risk of SPTB in IVF-conceived twin pregnancies compared to spontaneously conceived twin pregnancies is well established [12], data regarding TVU CL [13], and specifically studies assessing whether the increased risk of SPTB is predicted by a difference in CL, are limited.

The aim of this study was to compare the TVU CL at the midtrimester in screening for SPTB in asymptomatic IVF-conceived twin pregnancies compared to spontaneously-conceived twin pregnancies.

Materials and methods

This is a retrospective, single center, cohort study. All consecutive asymptomatic twin pregnancies who underwent TVU CL screening at University of Naples "Federico II" (Naples, Italy) at the time of routine second trimester fetal ultrasound exam at 18 0/7 − 23 6/7 weeks from January 2014 to January 2016 were included in the study. Monoamniotic twins, twin pregnancies with twin–twin transfusion syndrome, cerclage already in place, as well as major fetal malformations were excluded. Fetal reduction or spontaneous demise to twins, as well as twin pregnancies with one fetal demise before delivery were also excluded from the analysis. Therefore, the analyzed cohort included uncomplicated asymptomatic twin pregnancies with viable twins at the time of delivery. Type of conception was recorded and analyzed. Women were therefore divided in two groups: IVF-conceived twin pregnancies (i.e. IVF, intracytoplasmic sperm injection (ICSI), third party assisted ART); and spontaneously-conceived twin pregnancies. Women who underwent intrauterine insemination and those who received only medical treatment (e.g. clomiphene) but not IVF were excluded from the study. Surrogates and gestational carriers were also excluded. To avoid selection bias, all consecutive twin pregnancies who received TVU CL screening were included and analyzed.

Potential study subjects were identified at the time of a routine second trimester fetal ultrasound exam at 18 0/7 to 23 6/7-week gestation. Only TVU screening was employed for cervical screening, and only one TVU CL measurement was performed. Physicians who performed TVU CL screening were certified through the Fetal Medicine Foundation (FMF). Briefly, the measurement of CL was performed in the sagittal plane, visualizing the full length of the cervical canal from the internal os to the external cervical os. At least three measurements were obtained and the shortest was recorded [14,15]. Chorionicity was assessed using the lambda sign in the first trimester [16].

According to our protocol, delivery was planned at 37–38 weeks for dichorionic twins, and at 36–37 weeks for monochorionic twins [17,18]. Indication for earlier delivery was recorded.

Bed rest, pessary, cerclage, or progesterone were not routinely recommended. In IVF-conceived women, luteal phase support treatment, including 400 mg vaginal progesterone daily, was used until 12 weeks of gestation.

The primary outcome was the mean of TVU CL. Distribution of CL was determined and normality was examined in both groups, and incidence of short cervix in several cutoffs ($\leq$30, $\leq$25, $\leq$15, $\leq$10, and $\leq$5 mm) was calculated. Receiver-operating characteristics (ROC) curve was used to assess the CL value predictive for SPTB $<$32 weeks. Sensitivity, specificity, positive and negative likelihood ratio (LR$+$ and LR$-$, respectively) were calculated for TVU CL $\leq$30 mm in prediction of SPTB $<$32 weeks. We also assessed the relationship of TVU CL with gestational age at delivery between IVF-conceived and spontaneously conceived twin pregnancies. Secondary outcomes were gestational age at delivery, incidence of PTB and of SPTB $<$34, $<$32, and $<$28 weeks, and indication for delivery.

Primary and secondary outcomes were compared between IVF-conceived twin pregnancies with spontaneously-conceived twin pregnancies.

Data are shown as means $\pm$ SD, or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square or Fisher's exact test. Comparisons between groups were performed with the use of the Mann–Whitney U test, to test group medians; and with the use of the *t*-test to test group means with SD. Outcomes were estimated with multivariate analyses.

Logistic regression, presented as unadjusted odds ratio (crude odds ratio (OR)) or adjusted odds ratio (aOR) or as mean difference (MD) with the 95% of confidence interval (CI), was performed. Adjusted analysis was performed to correct data for relevant baseline characteristics. All potentially relevant baseline characteristics were added to the model as covariates.

Relevant baseline characteristics included: age, BMI, parity, history of SPTB, chorionicity, and smoking. This analysis was performed to show robustness of our results [19].

Distribution of cervical length was determined and normality was examined by the Kolmogorov–Smirnov test. We also planned to assess the incidence of short TVU CL, defined as TVU CL ≤30 mm, in subgroup analysis in women with and without prior SPTB.

ROC curve to assess the CL value predictive for SPTB <32 weeks was plotted for both IVF-conceived and spontaneously conceived twin pregnancies. The area under the curve (AUC) was computed to evaluate the overall performance of the diagnostic test accuracy in prediction of SPTB <32 weeks [9,20]. The AUC of a ROC curve is a measure of the overall performance of a diagnostic test in accurately differentiating those cases with and those without the condition of interest [9,20]. Difference between the AUC of the ROC curve for the IVF-conceived twins and the AUC of the ROC curve for the spontaneously conceived twins were calculated by using the DeLong nonparametric test [20]. The DeLong test assessed the standard error of the AUC and the difference between the two AUCs [20].

The correlation between CL and gestational age at delivery in IVF-conceived and spontaneously conceived twin pregnancies was assessed with the use of the Spearman's correlation coefficient. Comparison of coefficients was done by using the Fisher's Z-transformation. ANCOVA analysis of covariance was used to plot the general linear model for the relationship between CL and gestational age at delivery and the MD in weeks, between IVF-conceived and spontaneously conceived twins, was calculated. We calculated two-sided p-values. A p-value $< .05$ was considered to indicated statistical significance. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc, Armonk, NY).

This study was approved by the local IRB at University of Naples "Federico II" (#214/15).

Results

Characteristics of the study population

Overall, 668 women with diamniotic twin pregnancies, who underwent TVU CL screening between 18 0/6 and 23 6/7 weeks, were analyzed. Table 1 shows the characteristics of the 668 included women. 158 (23.7%) were IVF-conceived pregnancies, and 510 (76.3%) were spontaneously conceived pregnancies. In the IVF-conceived group, most of the women underwent conventional IVF, eight women underwent ICSI, and

Table 1. Characteristics of the included women with twin pregnancies.

	IVF-conceived N = 158 (23.7%)	Spontaneously-conceived N = 510 (76.3%)	p value
Maternal age			
Mean ± SD	30.2 ± 5.4	31.4 ± 6.3	.27
>35 y n (%)	40 (25.3%)	129 (25.8%)	.42
BMI			.72
Mean ± SD	25.7 ± 3.9	25.4 ± 4.2	
Nulliparity			.61
n (%)	92 (58.2%)	306 (60.0%)	
Prior SPTB			.81
n (%)	11 (7.0%)	40 (7.8%)	
Smoking			.84
n (%)	31 (19.6%)	102 (20.0%)	
Chorionicity n (%)			.84
Dichorionic	125 (79.1%)	408 (80.0%)	
Monochorionic diamniotic	33 (20.9%)	102 (20.0%)	
Type of ART n (%)		–	–
IVF	148 (93.7%)		
ICSI	8 (5.1%)		
Third party assisted ART			
Egg donation	2 (1.2%)		
Sperm donation	0 (0.0%)		

ART: assisted reproductive technology; SD: standard deviation; SPTB: spontaneous preterm birth; BMI: Body mass index; IVF: *in vitro* fertilization; ICSI: intracytoplasmic sperm injection.

two had egg-donor. Indication for IVF was various including endometriosis, tubal factor, male factor, or unexplained infertility.

The maternal demographics were not significantly different between the two groups. The mean maternal BMI was about 25 in both groups, and the mean maternal age about 30 years. Eleven women in the IVF-conceived group (7.0%), and 40 women in the spontaneously conceived group (7.8%) had history of SPTB. No women received progesterone, cerclage, or pessary during pregnancy for prevention of SPTB. Bed rest and activity restriction were not recommended in any of the included women.

Cervical length measurement

The mean gestational age at TVU CL was about 21 weeks in both groups. The mean TVU CL was significantly lower in the IVF-conceived group (32.2 ± 10.5) compared to the spontaneously-conceived group (34.1 ± 9.1) (MD −1.90 mm, 95%CI −3.72 to −0.08). Figure 1 shows the distribution of TVU CL in both groups. In IVF-conceived and in spontaneously conceived pregnancies, the 5th percentile were 7.9 and 18.0 mm, respectively; and the 95th percentile were 45.0 and 48.0 mm, respectively.

The incidence of short TVU CL, defined as TVU CL ≤30 mm, was 30.4% (48/158) in the IVF-conceived group and 21.6% (110/510) in the spontaneously-conceived group (aOR 1.59, 95%CI 1.06–2.37) (Table 2).

The incidence of short CL was still significantly higher in IVF-conceived group compared to the spontaneously-conceived group in both subgroup analyses of women with prior SPTB [4/11 (36.4%) versus 7/40 (17.5%); aOR 2.69, 95%CI 1.33–4.77] and without prior SPTB [44/147 (29.9%) versus 103/470 (21.9%); aOR 1.52, 95%CI 1.09–2.31].

On ROC curve analysis, TVU CL for the prediction of PTB <32 weeks showed an area under the curve of 0.73 (95%CI 0.61–0.85) in the spontaneously-conceived group (Figure 2), and of 0.82 (95% 0.70–0.94) in the IVF-conceived group (Figure 3). TVU CL in IVF-conceived twin pregnancies had a better value compared to TVU CL in spontaneously-conceived twin
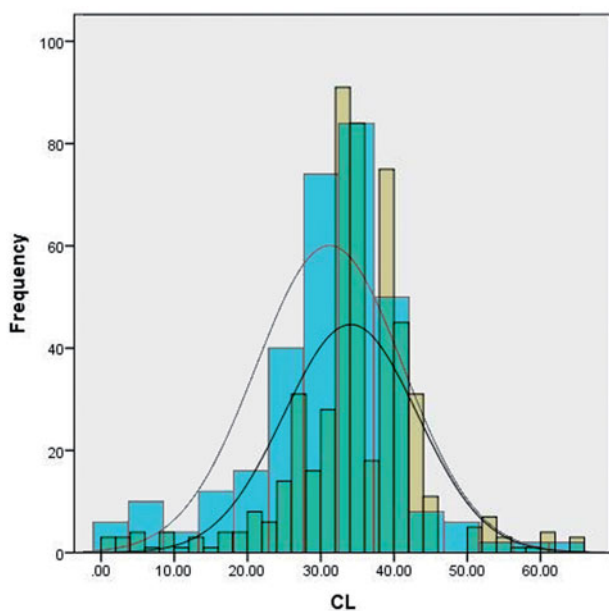
Figure 1. Distribution of transvaginal cervical length between 18 0–7 and 23 6/7 weeks in twins pregnancies. Yellow (thinner) boxes show spontaneously conceived twin pregnancies and blue (larger) boxes in transparency show IVF-conceived twin pregnancies. CL: cervical length.

pregnancies in prediction of SPTB <32 weeks (DeLong test: difference between areas 0.086, standard error 0.067, 95%CI 0.031–0.073, $p = .002$). Sensitivity, specificity, LR+ and LR−, for TVU CL ≤30 mm in prediction of SPTB <32 are shown in Table 3.

Relationship between cervical length and gestational age at delivery

Figure 4 shows the relationship between TVU CL and gestational age at delivery. For any given CL measured between 18 0–7 and 23 6/7 weeks, gestational age at delivery for IVF-conceived twins was earlier by about 1 week on average compared with spontaneously-conceived twins (MD −1.1 weeks; ANCOVA $p < .001$).

For TVU CL measurement assessed between 18 0/7 and 23 6/7 weeks, the correlation with gestational age at delivery in IVF-conceived twins was relatively constant [Spearman's correlation coefficient 0.62 (0.42–0.76)] and was statistically stronger (Fisher's Z-transformation $p = .01$) than in spontaneously-conceived twins [Spearman's correlation coefficient 0.31 (0.25–0.49)].

Pregnancy outcome

The gestational age at delivery was significantly earlier in the IVF-conceived group compared to the spontaneously conceived group by about 2 weeks (MD −2.31 weeks, 95%CI −2.74 to −1.33). IVF-conceived twin pregnancies had a significantly higher risk of PTB <34 and <32 weeks. The results did not change when iatrogenic births were excluded. Moreover, the IVF-conceived group had a higher incidence of delivery due to spontaneous onset of labor compared to spontaneously-conceived twin pregnancies (64.5 versus 54.9%; aOR 1.50, 95%CI 1.03–2.17) (Table 4).

Table 2. Cervical length measurement of the IVF-conceived and spontaneously-conceived twin pregnancies.

|	IVF-conceived N = 158 (23.7%)	Spontaneously-conceived N = 510 (76.3%)	aOR or MD (95%CI)[a]
GA at TVU CL assessment (weeks)			
Mean ± SD	21.7 ± 6.9	21.5 ± 4.3	0.20 weeks (−1.41 to 1.82)
TVU CL (mm)			
Mean ± SD	32.2 ± 10.5	34.1 ± 9.1	**−1.90 (−3.72 to −0.08)**
>30 mm	110 (69.6%)	400 (78.4%)	**0.63 (0.42 to 0.94)**
≤30 mm	48 (30.4%)	110 (21.6%)	**1.59 (1.06 to 2.37)**
≤25 mm	28 (17.7%)	56 (11.0%)	**1.75 (1.07 to 2.86)**
≤20 mm	19 (12.0%)	33 (6.5%)	**1.98 (1.09 to 3.58)**
≤15 mm	13 (8.2%)	20 (3.9%)	**2.20 (1.07 to 4.52)**
≤10 mm	8 (5.1%)	15 (2.9%)	1.76 (0.73 to 4.23)
≤5 mm	6 (3.8%)	10 (2.0%)	1.97 (0.71 to 5.52)

IVF: in vitro fertilization; GA: Gestational age; TVU CL: Transvaginal ultrasound cervical length; SD: standard deviation; CI: confidence interval; MD: mean difference; aOR: adjusted odds ratio.
Boldface data are statistically significant.
[a]Adjusted for all variables reported in Table 1.
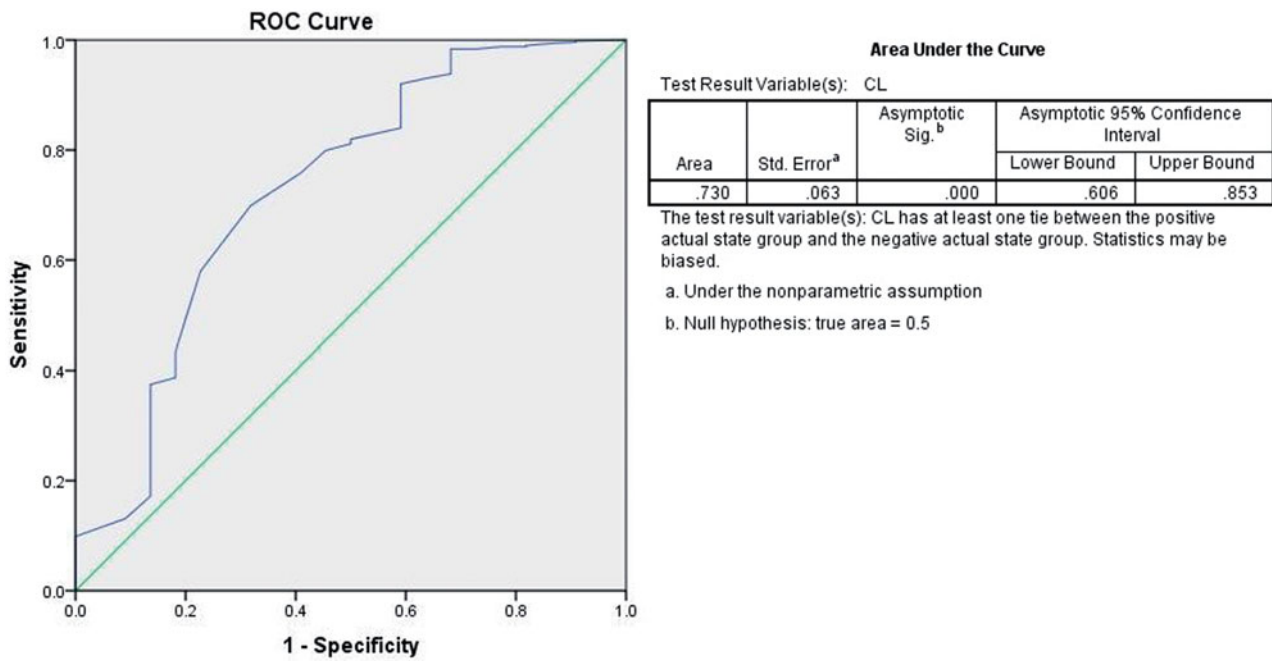
Figure 2. Receiver-operating characteristics curve showing predictive ability of cervical length for preterm birth <32 weeks in spontaneously-conceived pregnancy.
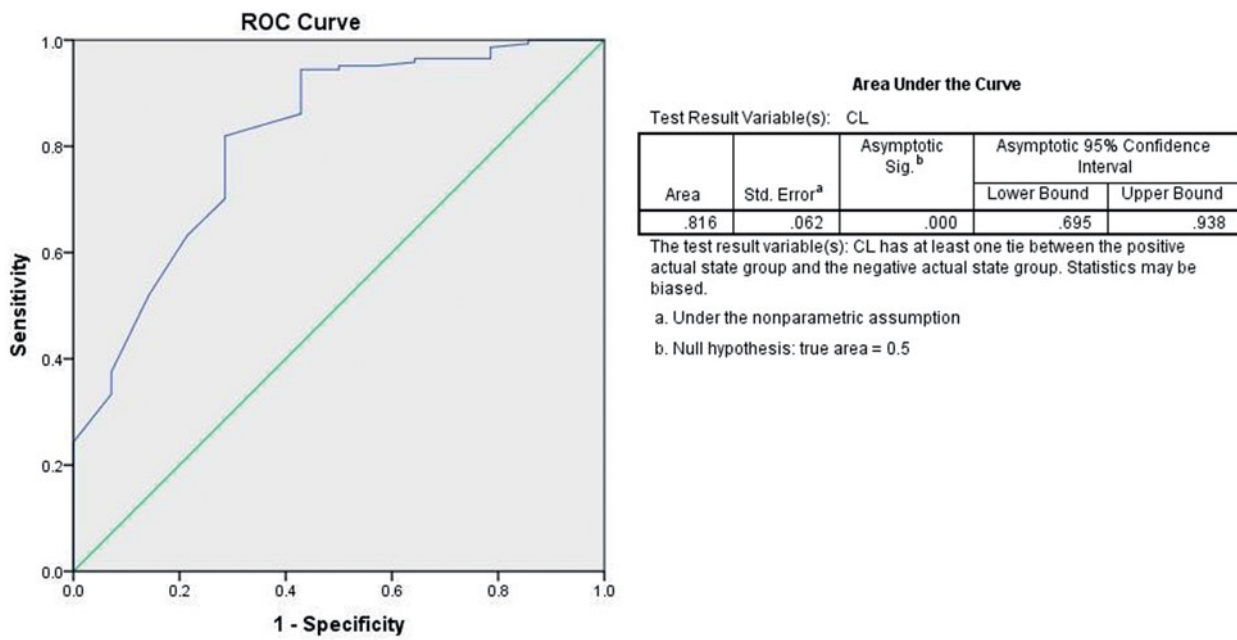
Figure 3. Receiver-operating characteristics curve showing predictive ability of cervical length for preterm birth <32 weeks in IVF-conceived pregnancy.

Discussion

This retrospective cohort study, including 668 women, showed that IVF-conceived diamniotic twin pregnancies had a higher rate of SPTB <34 weeks compared to spontaneously-conceived diamniotic twin pregnancies. This higher rate of SPTB was reflected by a lower mean midtrimester TVU CL and by an earlier mean

gestational age at birth, by about 1 week, per any given TVU CL in IVF-conceived compared to spontaneously-conceived pregnancies. IVF-conceived diamniotic twins had a higher rate of short cervix. The incidence of short CL was higher in the IVF-conceived group compared to the spontaneously-conceived group in both women with and without prior SPTB.

For any given CL measured between 18 0–7 and 23 6/7 weeks, gestational age at delivery for IVF-conceived twins was earlier by about 1 week compared with spontaneously-conceived twins.

This study has several strengths. TVU CL measurements were assessed by certified operators and were performed transvaginally. To our knowledge, there are no similar studies in the literature comparing TVU CL in IVF-conceived versus spontaneously-conceived diamniotic twin pregnancies. We excluded women with twin–twin transfusion syndrome. All women included in the analysis did not receive any therapy, such as bed rest, progesterone, cerclage or pessary [21,22], for PTB prevention. Therefore, our findings may reflect the natural history of twin gestations in regarding of PTB according to type of conception. The most important limitation of our study was the retrospective design. The CL was assessed only once between 18 0–7 and 23 6/7 weeks. Therefore, comparing the rate of cervical shortening during gestation was not feasible. Preparation and luteal support treatment in IVF-conceived twins with the early use of progesterone until 12 weeks of gestation could have modified the observed association. However, this seems unlikely given both its early administration and discontinuation, and not at gestational ages at which progesterone use has been studies in the prevention of SPTB [23–26]. Women who conceived via assisted conception may have underlying disease that could have influenced the pregnancy outcome.

The ability to identify women with twin gestations at highest risk of SPTB by second trimester TVU CL could allow for pregnant women to undergo targeted interventions, such as for example vaginal progesterone, or cerclage. TVU CL has been shown to be a good predictor of SPTB in asymptomatic twin gestations [27]. A meta-analysis of 21 studies, including 3523 women, showed that in asymptomatic twins a midtrimester TVU CL ≤ 30 mm have a pooled sensitivities, specificities, and positive and negative likelihood ratios in prediction of PTB <32 and <34 weeks of 65 and 56, 78 and 81, 3.0 and 3.0, and 0.45 and 0.55, respectively [27]. Our study showed that the higher rate of SPTB among IVF-conceived twins could be reflected and predicted by the higher rate of short TVU CL. This may support the theory that the pathogenesis for SPTB in twins might be different in the different populations.

Table 3. Sensitivity and specificity for each cervical length measurement with 95% confidence interval in prediction of spontaneous preterm birth <32 weeks in IVF-conceived and spontaneously-conceived twin pregnancies.

	Sensitivity (95%CI)	Specificity (95%CI)	LR+	LR−
IVF-conceived				
CL				
≤ 30 mm	71% (56–79)	74% (71–80)	2.7 (2.4–3.7)	0.4 (0.3–0.6)
Spontaneously-conceived				
CL	CL	CL	CL	CL
≤ 30 mm	54% (48–66)	80% (77–91)	2.7 (1.7–7.7)	0.6 (0.4–0.7)

CL: cervical length; CI: confidence interval; LR+: positive likelihood ratio; LR−: negative likelihood ratio; IVF: *in vitro* fertilization.
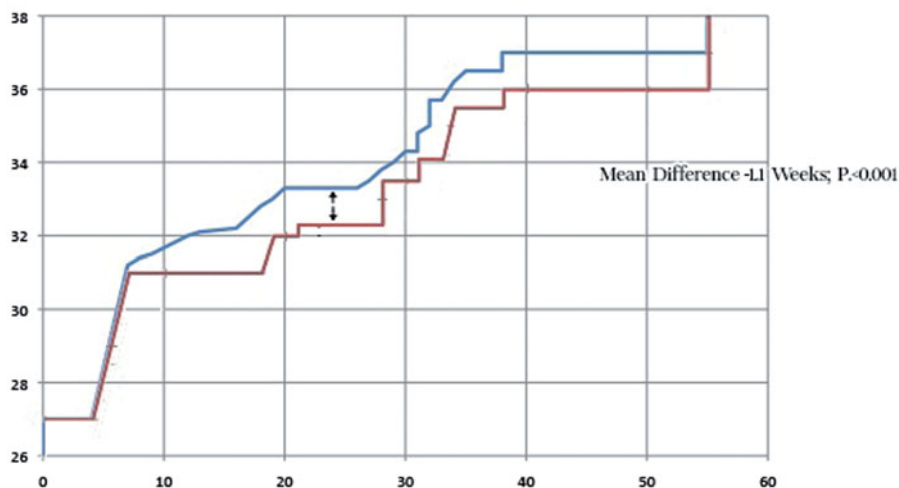
Figure 4. Relationship between cervical length between 18 0–7 and 23 6/7 weeks and gestational age at delivery in IVF-conceived and in spontaneously conceived twins. The relationship is presented for IVF-conceived twins (red – superior - line) and spontaneously-conceived twins (blue – lower - line). X-axis, cervical length (in mm); Y-axis, gestational age at delivery (in weeks). Mean difference −1.1 weeks; ANCOVA analysis of covariance $p < .001$.

Table 4. Pregnancy outcomes of the IVF-conceived and spontaneously-conceived twin pregnancies.

	IVF-conceived N = 158 (23.7%)	Spontaneously-conceived N = 510 (76.3%)	Crude OR (95%CI)	aOR or MD (95%CI)[a]
GA at delivery (weeks), Mean ± SD	33.0 ± 3.3	35.3 ± 2.4	–	**−2.31 weeks (−2.74 to −1.33)**
PTB <34 weeks n (%)	57 (36.1%)	122 (23.9%)	**1.85 (1.33–2.06)**	**1.79 (1.22–2.63)**
PTB <32 weeks n (%)	20 (12.7%)	51 (10.0%)	**1.36 (1.03–2.11)**	1.30 (0.75–2.26)
PTB <28 weeks n (%)	9 (5.7%)	21 (4.1%)	1.45 (0.94–2.49)	1.41 (0.63–3.14)
SPTB <34 weeks n (%)	52 (32.9%)	108 (21.2%)	**1.95 (1.33–2.41)**	**1.83 (1.23–2.71)**
SPTB <32 weeks n (%)	17 (10.8%)	49 (9.6%)	**1.21 (1.11–2.01)**	1.13 (0.63–2.03)
SPTB <28 weeks n (%)	5 (3.2%)	18 (3.5%)	1.03 (0.94–1.97)	0.94 (0.41–2.14)
Indication for delivery n (%)				
Maternal indication	30 (19.0%)	63 (12.4%)	**1.71 (1.11–2.14)**	**1.66 (1.03–2.68)**
Fetal indication	12 (7.6%)	40 (7.8%)	0.95 (0.40–2.01)	0.97 (0.49–1.89)
Combined	3 (1.9%)	2 (0.4%)	4.92 (0.81–29.69)	3.33 (0.75–29.69)
Planned at term	11 (7.0%)	125 (24.5%)	**0.23 (0.12–0.44)**	**0.33 (0.20–0.55)**
Spontaneous onset of labor	102 (64.5%)	280 (54.9%)	**1.66 (1.21–1.99)**	**1.50 (1.03–2.17)**

IVF: in vitro fertilization; GA: Gestational age; SD: standard deviation; PTB: preterm birth; SPTB: spontaneous preterm birth; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; MD: mean difference.
Boldface data are statistically significant.
[a]Adjusted for all variables reported in Table 1.

Our study also showed that any given TVU CL was associated with lower gestational age of about 1 week in the IVF-conceived group compared to the spontaneously-conceived group. Future studies should differentiate TVU CL and perinatal outcomes between IVF-conceived and spontaneously-conceived twin pregnancies. This information would be useful in counselling women regarding their risk of SPTB as well as improving the design of future studies evaluating therapies in the prevention of preterm delivery in twin pregnancies.

The biological plausibility to explain our findings are likely heterogeneous and complex. However, at least four hypotheses can be proposed. First, some unknown factors may be more likely to trigger subclinical or overt uterine contractions in IVF-conceived compared to spontaneously-conceived twin gestations, which would increase the risk of SPTB in the presence of a given CL measurement.

Second, IVF-conceived women may be more likely to undergo surgical procedures prior to pregnancy, including laparoscopy, hysteroscopy, as well as uterine evacuation which can damage the cervix, making it weaker and shorter during the pregnancy [28,29]. A recent meta-analysis, including 1,047,683 women, showed that prior abortion is an independent risk factor for PTB, due to the detrimental effect of cervical dilation for termination of pregnancy or curettage [30]. The increased risk of PTB could result from the subclinical inflammation and/or infection following the invasive diagnostic procedures, the oocyte pick-up or the embryo transfer, as well as from the mechanical trauma to the cervix, leading to increased risk of cervical insufficiency [30].

Third, women undergoing IVF are more likely to be affected by endometriosis [29], which has been correlated with an increased risk of PTB [29].

Fourth, compared to spontaneously conceived pregnancies, IVF-conceived pregnancies have higher circulating levels of relaxin [30], a polypeptide hormone linked to SPTB due to its effect on collagen breakdown [31]. Higher relaxin levels observed during pregnancy were significantly associated with SPTB [32,33].

In summary, our study showed that IVF-conceived twin pregnancies had a higher rate of SPTB than spontaneously-conceived twin pregnancies. The higher rate of SPTB in IVF-conceived twin pregnancies is associated with lower mean midtrimester TVU CL, as well as by the lower gestational age at birth per any given CL in the IVF-conceived compared to the spontaneously-conceived twin pregnancies.

Disclosure statement

The authors report no conflict of interest.

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