	Section Scar as Predictors for Preterm Labor in Patients with Previous Cesarean Section: A Prospective Cohort Study					
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#### ABSTRACT

**Background:** Cesarean sections (CS) have been increased all over the world. There is no doubt that CS scar from previous deliveries has an adverse effect on the function of the lower uterine segment (LUS) and the cervical canal length (CL). **Objective:** We examined the CL and thickness of lower uterine segment (LUS) by the antenatal ultrasound assessment to predict the occurrence of preterm birth (PTB).

**Materials and Methods:** This is a prospective cohort study (including women with previous CS and non-scarred uterus) by ultrasonography assessment of the LUS and CL was performed to all women at the time of recruitment (18–25 weeks) and was repeated in scheduled follow-up visits tell reach term pregnancy. The study conducted between February 2021 and August 2022. The number of cases with PTB was our primary outcome.

**Results:** Between the study (scarred uterus) n=140 and the control groups (non-scarred uterus) n=120 as regards age and body mass index (BMI) There were no significant differences. The study group showed a significant increase in PTB rate 26.1% (29/111) when compared to control group 11.8% (12/102) (p=0.008). The LUS in both groups had a significant thinning. However, the study group had more progressive thinning than the control group (5.25 ± 0.77 vs. 5.59 ± 0.80 mm, p= 0.001). According to CL, there was a progressive shortening of cervices in both groups.

**Conclusion:** The assessment of CL and LUS thickness during antenatal care visits may improve neonatal outcomes due to its safety and feasibility.

Key Words: Cervical length, cesarean section, lower uterine segment, preterm birth.

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#### **INTRODUCTION**

One of the main causes of neonatal morbidity and mortality in United States and all over the world is the Preterm birth (PTB). Over 385,000 infants are born prematurely in the United States per year<sup>[1]</sup>. babies delivered alive before completing 37 weeks of pregnancy are considered Preterm birth<sup>[2]</sup>. Respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and cardiovascular abnormalities are among neonatal morbidity associated with preterm birth<sup>[3]</sup>. The relative risk of preterm birth increased as the length of the cervix decreased<sup>[4]</sup>, when compared to non- scarred Women, those with scarred uterus were 14% increase to have a preterm birth in their second pregnancy compared to non-scarred uterus woman<sup>[5]</sup>.

Researchers found that in nations where cesarean rates are above 15%, populations having more neonatal, infant,

and maternal death rates. Cesarean sections babies are more requiring neonatal intensive care unit (NICU) care, having greater respiratory complications, higher odds of childhood asthma, and obesity<sup>[5]</sup>.

The cesarean scar increased risk of spontaneous PTB might be to the presence of(changed uterine microenvironment with or without increased inflammation, abnormal placental implantation, affected cervical function due to cervical damage during the prior CS, disruption or dehiscence of tissue, fluid or blood stasis in the lower uterine segment) that might cause the progress to PTB<sup>[2]</sup>.

In women with prior CS, the incidence of scar dehiscence (in the absence of uterine scar rupture) has been reported to be 3.2% and is associated with PTB<sup>[6]</sup>.

However, there is no precise test to identify women who will end up with PTB. Ultrasonographic assessment

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of lower uterine segment thickness and cervical length best identifies the risk for preterm birth. To the best of our knowledge, this study is the first to use thinnest part of LUS and CL as predictors of PTB.

## MATERIALS AND METHODS

#### Trial registration

The Ethics Committee of Assiut University approved this study by (IRB No 17101329, registration date: 18/09/2020) and The Clinical Trials Registry was registered by (NCT04554745).

### Study participants

This is a prospective cohort study conducted at Women Health Hospital, Assiut University, Egypt in the period from February 2021 up to August 2022. Inclusion criteria included: singleton pregnancies, inter-pregnancy interval (18-59 months), and maternal age between 18-35 years. Patients with prior history of PTB, multiple pregnancies, preeclampsia, major fetal abnormalities, history of cervical surgery, uterine anomalies, placental abnormalities (placenta previa, accreta, placental abruption), indicated preterm births with medical disorders (diabetes mellitus or hypertension) were excluded.

### Study outcomes

The number of cases with PTB in scarred uterus group was our primary outcome and the Secondary outcomes were to detect maternal morbidities (PROM) and neonatal morbidities (neonatal pediatric care unit admission, birth weight, respiratory distress, and gestational age).

#### Ultrasound assessment of LUS and CL

We followed up the study group (scarred uterus) and control group (non-scarred uterus) with two ultrasound visits. Measuring of CL and LUS at recruitment 18 0/7 -25 6/7 weeks and then followed up visits at 28 0/7 32 6/7 weeks. TAUS measuring of LUS by using Medison SONOACE X6 ultrasound. To ensure accurate imaging of the LUS, the test was performed with the patient's bladder completely full. To visually locate the thinnest part of the lower segment at the midsagittal plane along the cervical canal, the LUS was examined longitudinally and transversally. This area was at least enlarged to the point where any caliper movement would result in a measurement shift of no more than 0.1 mm. The myometrium/chorioamniotic membrane/amniotic fluid and the urinary bladder wall-myometrium interfaces were measured with calipers<sup>[7]</sup> (Figure 1).



Fig. 1: (A): TAUS measurement of LUS (B): TVUS measurement of CL

For transvaginal sonography, after voiding, and inserting the transducer in the anterior vaginal fornix and women were in the lithotomy position. Visualizing the cervix in the longitudinal plane, and the endocervical mucosa was identified. Measuring the cervical length as the length of the endocervical mucosa from the internal to the external os. The whole cervical canal was visualized with attention to avoid aggressive pressure on the cervix and artificial lengthening<sup>[8]</sup>. To achieve this result, the operator visualizes the whole canal and then withdraws the probe gently until visualizing the internal os. If accidentally a funnel at the internal os discovered, the length was measured from the apex of the funnel (functional internal os, where met the closed endocervical canal) to the external os (Figure 2).



Fig. 2: flow chart of the study and control group

#### Statistical analysis

We analyzed Data by using SPSS program (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Qualitative data were statistically described in the form of mean  $\pm$  SD, and median (range) while qualitative data were statistically described in form of number (percentage). Comparison of quantitative variables was done using Student t-test and paired sample t test for paired data. For comparing categorical data, Chi<sup>2</sup>-test was used.

### RESULTS

### **Baseline characteristics**

A total of 260 participants were deemed eligible for our study of which 213 participants were included (Figure 2).

Demographics of the included participants were detailed in (Table 1).

### Preterm birth outcomes

Delivery outcomes were available for 213 women. The overall rate of PTL<37weeks was 19.2% (N=41/213). The rate of early preterm birth<34weeks was 4.7% (N=10/213) and late preterm birth was 14.5% (N=31/213). The rate of PTB in the studied group was 26.1% versus 11.8% in the control group. Between both the studied groups, there were no significant differences regarding age, residence, education, employment, and body mass index with.

# Changes in the thickness of lower uterine segment and cervical length

We reported no significant difference between examined groups at time of recruitment regarding LUS and CL assessment. However, at the second visit (28-

Table 1: Demographic data of the study and control groups

32 weeks); both groups showed significant thinning of LUS (P<0.001). The degree of thinning of LUS was significantly higher among the study group ( $5.25\pm0.77$  vs.  $5.59\pm0.80$ mm, P=0.001). Regarding CL, we reported no significant difference between investigated groups at baseline and second visit (P=0.205, and P=0.434) respectively (Table 2).

## Maternal and neonatal outcomes

(Table 3) shows that the mean birth weight and gestational age were significantly higher in the control group compared to the study group (P<0.05). The rate of CS and preterm delivery were significantly higher in the study group (P<0.05). Apgar score, NICU admission, respiratory distress, and neonatal mortality were comparable between both the studied groups with no significant difference between them (P>0.05).

The Receiver Operating Curve (ROC) on the performance of screening for the preterm labor. By thinnest part of lower uterine segment at a cut-off value of  $\leq$ 5.9mm had a sensitivity of 53.66% and specificity of 59.88% in predicting preterm labor. By CL at a cut-off value of  $\leq$ 3.28cm had a sensitivity of 60.98% and specificity of 60.47% in predicting preterm labor.

Personal data		Study group, n= 140	Controls, n= 120	P-value <sup>1</sup>
Age: (years)				
•	$Mean \pm SD$	$28.96\pm3.56$	$28.18 \pm 4.70$	0.131
•	Range	22.3-35.3	18.4-35.8	
BMI:				
•	$Mean \pm SD$	$24.90\pm2.85$	$25.02\pm2.86$	0.727
•	Range	20.2-29.6	20.1-30.0	
Residence:				
•	Urban	48.6%	45.8%	0.659
•	Rural	51.4%	54.2%	
Educat	ion:			
•	Illiterate	35.0%	31.7%	0.570
•	Secondary or more	24.3%	26.7%	0.660
•	basic	40.7%	41.7%	0.876
Employ	yment:			
•	yes	48.6%	49.2%	0.924

Quantitative data are presented as mean  $\pm$  SD and range. *P value*<sup>1</sup>: for comparing both studied groups, *P value*<sup>2</sup>: for comparing the same group overtime. *P value* set significant if <0.05.

A-thinnest part of LUS (mm)	Study group, n= 140	Controls, n= 120	P-value <sup>1</sup>
At recruitment (18-25 weeks)			
• Mean $\pm$ SD	6.07±0.99	6.27±0.95	0.111
• Range	4.1-9.4	4.1-8.8	
At second visit (28-32 weeks)	Study group, n= 120	Controls, n= 112	
• Mean $\pm$ SD	5.25±0.77	$5.59{\pm}0.80$	0.001
• Range	3.5-7.3	3.8-7.4	
<i>P-value</i> <sup>2</sup>	< 0.001	< 0.001	
Percent of change:			
• Median (Range)	12.1 (2.4-54.9)	9.4 (2.1-32.1)	0.001
B-cervical length(cm)	Study group, n= 140	Controls, n= 120	P-value <sup>1</sup>
At recruitment (18-25 weeks)			
• Mean $\pm$ SD	3.43±0.53	3.52±0.54	0.205
• Range	2.4-5.0	2.5-5.5	
At second visit (28-32 weeks)	Study group, n= 120	Controls, n= 112	
• Mean $\pm$ SD	3.15±0.55	3.21±0.52	0.434
• Range	2.0-4.6	1.8-4.8	
<i>P</i> -value <sup>2</sup>	< 0.001	< 0.001	
Percent of change:			
• Median (Range)	4.8 (0.8-98.3)	5.7 (0.3-91.0)	0.074

 Table 2: lower uterine segment and Cervical length of the study and control groups

Quantitative data are presented as mean  $\pm$  SD and range. *P* value<sup>1</sup>: for comparing both studied groups, *P* value<sup>2</sup>: for comparing the same group overtime. *P* value set significant if <0.05.

Table 3: Maternal and fetal outcomes of the study and control groups

Outcome	Study g	Study group, n= 140		Controls, n= 120	
Birth weight (gm)					0.043
• Mean $\pm$ SD	2823.4	$2823.42 \pm 467.91$		$2951.47 \pm 446.41$	
• Range	1200.0-3500.0		1100.0-4200.0		
Mode of delivery, n (%)					< 0.001
Cesarean section	108	97.3%	15	14.7%	
Vaginal delivery	3	2.7%	87	85.3%	
Gestational age at delivery:					< 0.001
• Mean $\pm$ SD	$37.23 \pm 1.48$		$38.33 \pm 1.93$		
• Range	30	30.6-39.4		28.3-40.9	
Term/ pre-term:					0.008
• Term	82	73.9%	90	88.2%	
• Pre-term	29	26.1%	12	11.8%	
Type of pre-term:					1
• Early pre-term (28-34)	7	24.1%	3	25.0%	
• Late pre-term (34-37)	22	75.9%	9	75.0%	
Apgar score at 5 min:					0.091
• <7	17	15.3%	8	7.8%	
• >7	94	84.7%	94	92.2%	
Admission to NICU:	18	16.2%	9	8.8%	0.105
Abortion at current pregnancy	3	2.6%	0	0.0%	0.246
Respiratory distress	18	16.2%	8	7.8%	0.092
Neonatal mortality at NICU:	2	1.8%	3	2.9%	0.672

#### DISCUSSION

Repeated CS accounts for about 40% of all cesarean surgeries. The consequences are not just pecuniary, but also in the form of neonatal and maternal morbidity. Neonates born to mothers who have intentional CS are at higher risk of respiratory morbidity<sup>[9]</sup>. Elective repeated CS are linked to large number of maternal problems including (blood transfusion, longer duration of hospital stays, intensive care unit admission, placenta accrete, visceral injury, and hysterectomy,)<sup>[10]</sup>.

Data from numerous research indicates that assessing cervical conditions such as CL can predict preterm birth. TVUS-CL has recently been the primary method for assessing threatened preterm labor. in both second and third trimesters, TVUS-CL is one of the most commonly marker for PTB prediction<sup>[11-13]</sup>.

The current study aimed to use the CL and the thickness of CS scar as predictors for preterm birth in patients with previous CS. The current study enrolled a total of 260 women; out of them 120 women hadn't previous CS while the other 140 women had previous CS.

Between the study and control groups, there was no significant difference regarding to different baseline and obstetric data (age, BMI, residence, education, employment, parity, history of abortion and duration from last pregnancy). Although both groups also had insignificant differences as regards CL. However, women of the study group had significantly lower thickness of LUS during the second visit.

The risk of uterine rupture at delivery or uterine scar dehiscence increases when there is thinning of LUS (a LUS thickness of less than 2.0 mm has a greater risk of uterine rupture). The first trimester ultrasound assessment of CS scar through the assessment of the residual myometrial thickness, may a good tool in early recognition of patients at risk of subsequent perinatal complications including uterine rupture<sup>[14]</sup>.

As regards fetal and maternal outcomes, we reported that the study group had significantly lower birth weight and significantly higher frequency of CS and PTB. But both groups had insignificant differences as regard neonatal mortality and admission to the NICU. Hu *et al.* stated that CS in the first pregnancy has a higher risk of repeated cesarean deliveries and adverse obstetric and perinatal outcomes in the following deliveries, especially in women without CS indications<sup>[15]</sup>.

There is still a lot of interest in the causes of PTB. Preterm birth has been widely thought to be a syndrome from multiple mechanical factors such as uterine over distension, inflammation (e.g. infection), uteroplacental ischemia, circulatory ddisturbances, or a combination of several factors)<sup>[16]</sup>.

In this study, a total of 213 singletons had follow-up at delivery. Out of this group, 41 (19.2%) women had PTB, and 172 (80.8%) women had full-term labor. The majority of PTB came from rural areas with significantly lower body mass index (BMI). Other baseline and obstetric data showed no significant differences between groups. Also, we discovered that both groups had insignificant differences as regard to baseline thickness of LUS but during follow up PTB group had significantly thinner LUS with a significantly higher percentage of reduction in the thickness of LUS compared to full-term group.

Also, PTB group had significantly lower CL at recruitment and during the 2nd visit in comparison to the term group, and higher percentage of reduction in CL with borderline significance.

Based on this study predictors for PTB were history of CS (OR=2.328) and decreasing of CL at recruitment (OR=0.422). At the cutoff point<5mm; LUS had 75.6% overall accuracy in the prediction of PTB while at the cutoff point <3.01cm; CL had 76.5% overall accuracy in the prediction of PTB.

Using LUS thickness < 4.5mm for prediction of preterm birth, Yapan *et al.* reported that the risk of preterm birth after adjustment of other factors was increased by 2.37 folds (p=0.037). Sensitivity, specificity, PPV, and NPV were 14% (95% CI: 6.64–25.02), 92.8% (95% CI: 90.06– 95.12), 22.5% (95% CI: 12.66–36.76) and 88% (95% CI: 86.92–89.08) respectively<sup>[17]</sup>.

In a previous study on twin pregnancy, there were 58 women at term delivery and 38 women at a preterm delivery. The authors reported that the cutoff value for LUS-MT was 4.26mm sensitivity 92.1%, specificity 86.2%, with the area under the ROC curve 0.917, with PPV 81.3%, NPV 94.3% and accuracy  $92.1\%^{[18]}$ .

Dziadosz *et al.* stated that the association of PTB <37 weeks and CL  $\leq$ 25mm with a sensitivity of 15% and a specificity of 98% (*P* <0.001; RR, 6.7). In the second trimester, CL  $\leq$ 25 mm was associated with PTB <34 weeks (*P* <0.001; RR, 7.7; specificity, 98%; sensitivity, 19%)<sup>[19]</sup>.

According to a recent study, the frequency of PTB decreased by 35 percent and the combined neonatal morbidity and mortality decreased by 40 percent by using vaginal progesterone therapy for women had a short cervix<sup>[20]</sup>.

Cervical length varies among different populations. The common example is that of African Americans have a significantly shorter CL compared to Caucasians, and this reported in various published studies<sup>[16, 21]</sup>.

Some women are getting prophylactic oral, vaginal, or intramuscular progesterone as preventive care of short cervix. We acknowledge that this may have had an impact on the number of spontaneous PTB, but it was unethically not to allow doctors to offer progesterone treatment when patient had a short cervix, especially when there still has evidence that this treatment may be effective in decreasing spontaneous PTB.

The strength of the present study was that it was a large prospective cohort study in singleton pregnancies using the LUS thickness and the CL measured by ultrasonography to predict PTB.

## CONCLUSION

The assessment of LUS and CL in women with repeated cesarean section (CS) seem to successively predict Preterm birth.

# **CONFLICT OF INTERESTS**

There are no conflicts of interest.

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