First trimester Uterine artery Doppler assessment and Cervical length measurement

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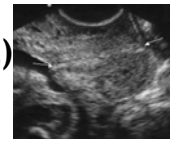
1. Uterine artery (UtA) doppler assessment

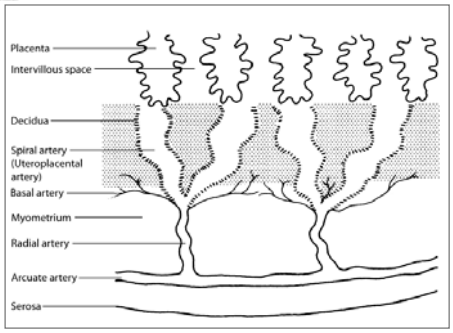
2. Cervical length (CL) measurement



Background

Uterine artery Doppler in the second trimester can predict 50%-85% of PE <34 weeks for a 5%-10% of false-positive rate

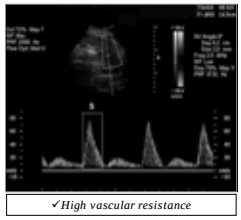
Background



Khong TY et al 1986 BJOG, 93:1049-1059

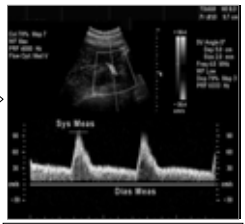
Placental implantation: effects on UtA Doppler

Non-pregnant



✓*High vascular resistance*

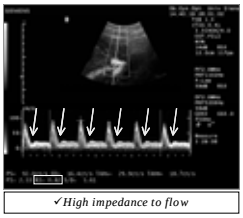
In pregnancy (20-24 sett.)



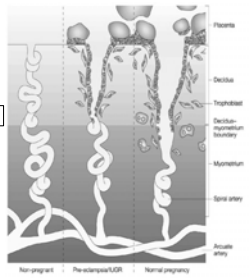
✓ *Reduced vascular resistance*

Placental implantation: effects on UtA Doppler

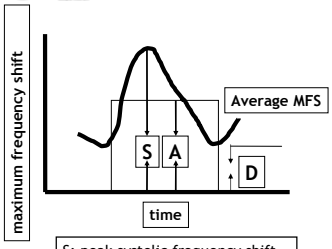
Abnormal pregnant uterine a.



✓*High impedance to flow*



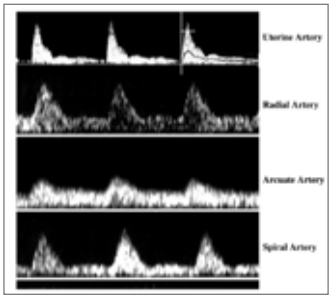
Doppler indices



S: peak systolic frequency shift
D: end-diastolic frequency shift
A: temporal averaged frequency shifts over one cardiac cycle

RI = (S-D)/S
[Pourcelot 1974]
PI = (S-D)/A
[Gosling 1976]
S/D ratio
[Stuart&Drumm 1980]
D/A ratio
[Maulik et al 1982]

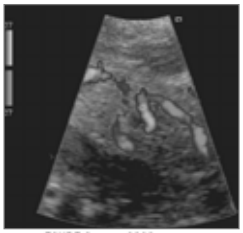
Waveform characteristics



Doppler waveforms obtained at 10 weeks' gestation

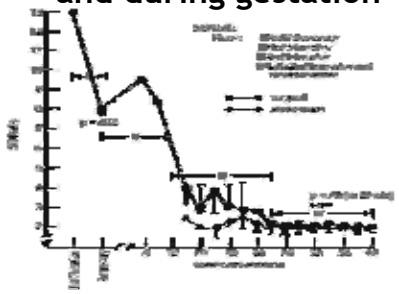
UtA visualization

Uterine artery visualized by transvaginal color flow mapping at the level of the cervicocorporeal junction, as used in the first trimester



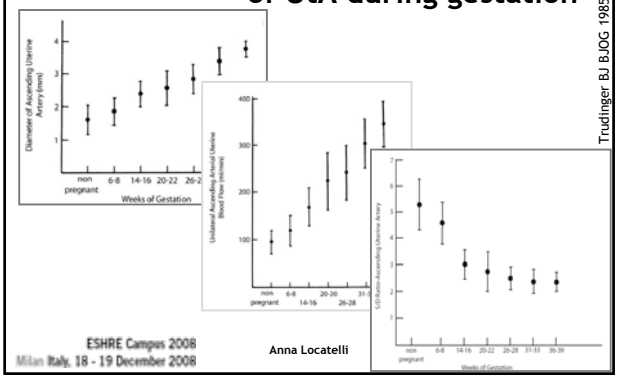
Uterine artery visualized by transabdominal color flow mapping at the crossover point with the external iliac artery, as used in the second trimester

Doppler indices before and during gestation



Jurkovic et al , Obst and Ginecol 1991;77, 365-69

Anatomical and flow modification of UtA during gestation



Trudinger BJ BJOG 1985;77

Mean UtA PI during gestation

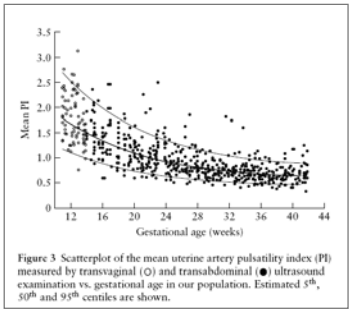
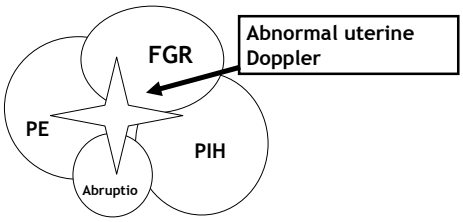


Figure 3 Scatterplot of the mean uterine artery pulsatility index (PI) measured by transvaginal (○) and transabdominal (●) ultrasound examination vs. gestational age in our population. Estimated 5th, 50th and 95th centiles are shown.

Gómez O. Ultrasound Ob Gyn 2008

UtA Doppler as indicator of placental vascular pathology independent of clinical manifestations

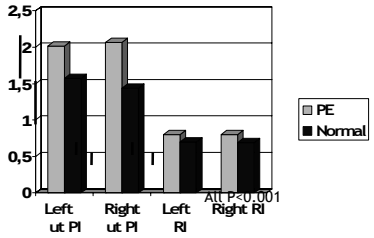


Aardema MW Clin Sci 2004;106:377-82

UtA Doppler screening in the 1st trimester: prediction of preeclampsia

Study 1 - Cohort of 592 women with uterine Doppler <u>at 12-16 weeks;</u>

4.7% developed PE



Harrington K. Ultrasound OG 1997

UtA Doppler screening in the 1st trimester: prediction of preeclampsia

Study 1 - Cohort of 592 women with uterine Doppler <u>at 12-16 weeks</u>

- Bilateral notches in 33%
  sensitivity = 93%
  specificity = 69% +LR = 3.0 (2.5-3.2)
- Adding uterine RI:
  specificity = 85% +LR = 6.2 (5.0-6.7)

Harrington K. BJOG 1997 & Ultrasound OG 1997

UtA Doppler screening in the 1st trimester: prediction of preeclampsia

Study 2 - Cohort of 3045 women with uterine Doppler at 11-14 weeks

- 2.1% developed PE
- Using mean uterine PI > 95th centile:

Screen pos. rate 5%
Sensitivity 27%
Specificity 95%
+LR 5.9 (3.7-8.8)

Martin AM. Ultrasound Ob Gyn 2001

UtA Doppler screening in the 1st trimester: prediction of preeclampsia

Study 3 - Cohort of 999 women with uterine Doppler at 11-14 weeks

- 2.2% developed PE
- Using mean uterine PI > 95th centile:

Screen pos. rate 5.3%
Sensitivity 24%
Specificity 95%
+LR 4.6 (95% CI 2.0-9.4)

Gómez O. Ultrasound Ob Gyn 2005

UtA Doppler screening in the 1st trimester: prediction of preterm PE

Study 4 - Cohort of 3324 women with uterine Doppler at 11-14 weeks

- 10 (0.3%) with PE delivered <32 weeks
- Using mean uterine PI > 95th centile:

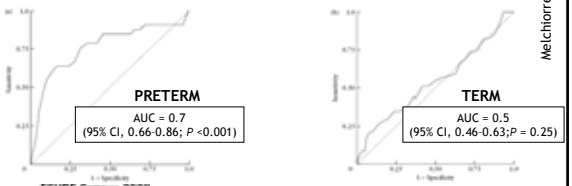
	PE delivered <32 wks
Screen pos. rate	5%
Sensitivity	60%
Specificity	95%
+LR	12.2 (6.3-17.2)

Martin AM. Ultrasound Ob Gyn 2001

UtA Doppler screening in the 1st trimester: for prediction of preterm PE

Study 5- Cohort of 3058 women with uterine Doppler at 11-14 weeks

- 33 with PE delivered <37 weeks
- 57 with PE delivered >37 weeks



Melchiorre UOG 2008

UtA Doppler screening in the 1st trimester: prediction of IUGR

Study 3 - Cohort of 999 women with uterine Doppler at 11-14 weeks

- 3.7% developed IUGR
- using mean uterine UtA PI > 95th centile:

Screen pos. rate	5.3%
Sensitivity	24.3%
Specificity	95.4%
+LR	5.3 (CI 2.7-9.5)

Gómez O. Ultrasound Ob Gyn 2005

UtA artery Doppler screening in the 1st trimester: prediction of any adverse outcome

Study 3 - Cohort of 999 women with uterine Doppler at 11-14 weeks

- 6.7% developed GH, PE, BW < 5th centile, abruptio or stillbirth
- Mean uterine PI > 95th centile:

screen positive rate	7.4%
sensitivity	31%
specificity	93%
+LR	5.6 (1.8-16.6)

Gómez O. Ultrasound Ob Gyn 2005

Recent review

- 74 studies of PE (total 79,547) and 61 studies of IUGR (total 41,131) to **April 2006**
- Low and high risk population, often overlap
- Low accuracy in high risk patients
- Better accuracy for severe/preterm PE than late PE and IUGR
- PI is the most predictive Doppler index in most cases

Crossen JS et al. CMAJ 2008;178:701-11.

Low risk

II trimester

	N° cases	Sens	Spec	LR+
Severe PE	15329	78%	95%	15.6 (13.3-17.3)
Overall PE	38230	42%	91%	4.5 (1.7-7.3)
Severe IUGR	1757	67%	95%	13.7 (10.3-16.9)
Overall IUGR	12097	18%	95%	3.4 (1.7-5.1)

I trimester

	N° cases	Sens	Spec	LR+
Severe PE	433	40%	90%	4.0 (1.6-7.3)
Overall PE	4966	25%	95%	5.4 (4.1-6.7)
Severe IUGR	999	24%	95%	5.3 (2.8-9.5)
Overall IUGR	3045	12%	96%	2.7 (1.9-3.8)

High risk

II trimester

	N° casi	Sens	Spec	LR+
Severe PE (RI)	28	80%	78%	3.7 (1.4-5.3)
Overall PE	547	39%	78%	1.8 (0.2-3.4)
Severe IUGR	351	6%	95%	13.7 (10.3-16.9)
Overall IUGR	445	58%	75%	2.3 (1.0-3.6)

I trimester

	N° casi	Sens	Spec	LR+
Overall PE (only notching)	72	91%	46%	1.7 (1.1-1.9)
Overall IUGR	785	34%	76%	1.5 (1.0-1.9)

First trimester UtA Doppler: recent studies

	N	Cut-off
Martin et al. 2001	3,045	PI >95th centile
Gomez et al. 2005	1,091	PI >95th centile
Dugoff et al. 2005	1,067	RI 75th centile RI ≥90th centile RI ≥95th centile
Parra et al. 2005	1,447	PI >95th centile
Pilalis et al. 2007	1,123	PI ≥95th centile
Plasencia et al. 2007	6,015	PI ≥90th centile
Melchiorre et al. 2008	3,058	RI ≥90th centile

Sensitivity

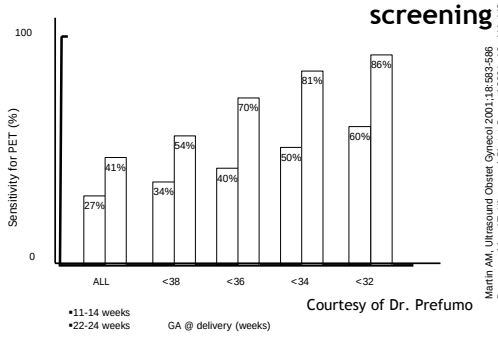
24-27% PE

33-67% Early-onset PE

12-25% SGA

Courtesy of Dr. Prefumo

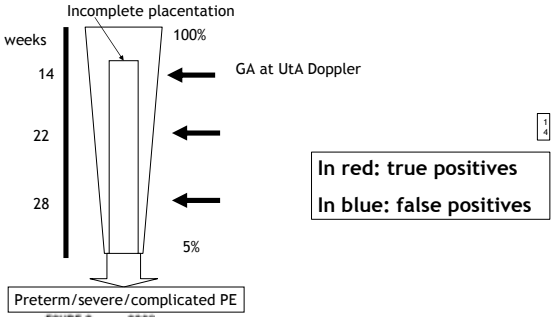
2nd trimester UtA Doppler screening performs better than 1st trimester screening



Martin AM, Ultrasound Obstet Gynecol 2001;18:583-586
Papageorghiou AT, Ultrasound Obstet Gynecol 2001; 18: 441-449

Courtesy of Dr. Prefumo

Rationale for observed findings



In red: true positives

In blue: false positives

How can we improve predictive ability in low risk women?

1. add serum markers

- **PP-13** Nicolaides KH Us Ob Gyn 2006
- **Neurokinin B (NKB)** Page N. Nature 2000
- **PAPP-A** Dugoff for FASTER
  Spencer Prenat Diagn 2005
- **Others: hCG, endoglin, TGF-ß1, PlGF , sFlt1, sVEGFR-1**

How can we improve predictive ability in low risk women?

2. Add maternal cardiac function

(534 nulliparous)

- **LOW or HIGH Cardiac output?**
- **HYPERDINAMIC status or high RESISTENCE?**

Khaw BJOG 2007

Table 3. Differences in maternal central and peripheral haemodynamics between the uncomplicated pregnancies and those complicated by pre-eclampsia without SGA, pre-eclampsia with SGA and SGA alone

Variable	Pre-eclampsia no-SGA	Pre-eclampsia with SGA	SGA
MAP (mmHg)	↑	↑	↔
Total vascular resistance (dynes/sec/cm^5)	↔	↑	↑
UAPI	↔	↑	↑
Left ventricular systolic function			
Stroke volume (ml)	↑	↔	↓
Cardiac output (L/min)	↑	↔	↔
Cardiac index (L/min/m^2)	↑	↔	↔
Mitral valve annulus shortening (mm)	↑	↔	↔
Left ventricular diastolic function			
Transmitral E-wave velocity (mm/sec)	↑	↔	↔
Transmitral A-wave velocity (mm/sec)	↔	↔	↔

Table 4. Logistic regression models for prediction of pre-eclampsia and birthweight below the tenth centile

Variable	Coefficient	Odds ratio (95% CI)	*P*-value
Pre-eclampsia			
MAP	0.14	1.15 (1.09–1.22)	<0.0001
Stroke volume	0.03	1.03 (1.0–1.07)	0.04
UAPI	1.45	4.26 (2.03–8.95)	<0.0001
Birthweight below tenth centile			
Stroke volume	−0.04	0.95 (0.92–0.98)	0.001
UAPI	1.26	3.52 (2.0–6.19)	<0.0001

How can we improve predictive ability in low risk women?

3. Sequential change

UtA Doppler <u>at 11-14 weeks and at 19-22</u> in 870 women
7.3% developed gestational hypertension, PE or BW < 5th centile

Table 3 Mean and SD for mean uterine artery pulsatility index (PI) and prevalence of a bilateral notch in normal and complicated pregnancies

Gestational week	n	PI Mean	PI SD	Bilateral notch (%)
11–14				
Normal outcome	806	1.74	0.54	40.9
Complicated pregnancy	64	2.32	0.72	59.4
		$P < 0.001$* →		$P < 0.001$†
19–22				
Normal outcome	806	1.09	0.30	11.3
Complicated pregnancy	64	1.34	0.43	32.8
		$P < 0.001$* →		$P < 0.001$†

*Independent samples t-test. †Chi-square test.

Differences in mean PI between complicated and normal group :

- **0.37 (95% CI, 0.24-0.52) I trim**
- **0.25 (95% CI, 0.17-0.33) II trim**

Gómez UOG 2006 (5)

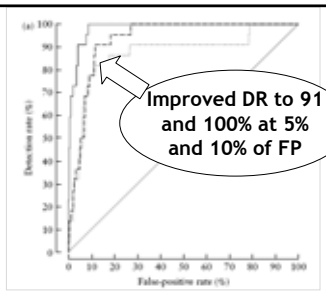
How can we improve predictive ability in low risk women?

4. Sequential change and maternal risk factors

Cohort of 3107 women with uterine Doppler at 12 and at 23 weeks

- 93 (3.0%) developed PE (22 - 0.7% early <34wks and 71 -2.3% late PE, 73 (2.3%) GH, 346 (11.1%) SGA
- Individual risk calculated with:
  1. UtA Doppler
  2. PI ratio II trimester / I trimester
  3. maternal factors (CH, parity, ethnicity)

Nicolaides K. H. UOG 2008



Screening for early PE by
- UtA PI I trimester (. . .),
- maternal factors and PI I trimester (- - -),
- maternal factors, PI I trimester and ratio II /I trimester (__).

What can we propose to women identified as at risk?

- 86 women at HR for PE (age, family Hx of PE, DM, cHTN, Hx of PE, FGR or IUFD)
- Uterine Doppler at 12-14 weeks
- If abnormal (bilat. notches, 75%) → RCT of ASA 0.5 mg/kg

Vainio M. BJOG 2002

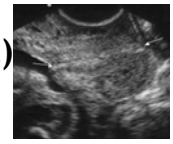
	Preeclampsia		RR	95% CI
	Aspirin	Placebo		
Total	4.7% (2/43)	23% (10/43)	0.20	0.05-0.86

Conclusions 1
UtA Doppler

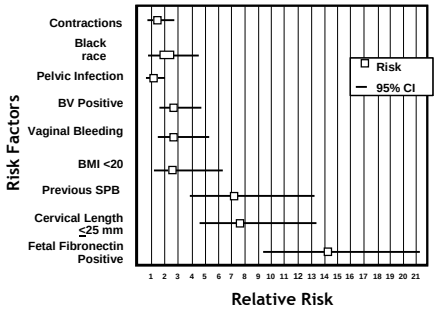
- Placentation is a process starting early that could be studied early
- UtA Doppler similar in I and II trimester
- Not perfect diagnostic indices, importance of false negative and false positive
- Future use of combination of tests

1. Uterine artery (UtA) doppler assessment

2. Cervical length (CL) measurement



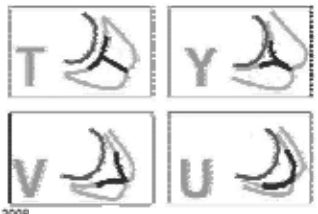
Background
Relative risk of PTD <32 wks



Goldenberg RL et al. *Am J Public Health*. 1998;88:233-238.

Background

- Different strategies to predict preterm delivery in symptomatic and asymptomatic patients
- One of this strategy uses transvaginal sonography (TVS) to measure and examine the length and shape of the cervix



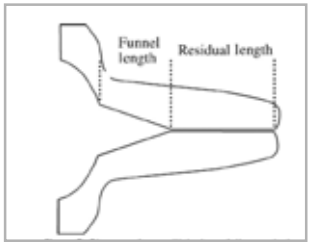
Iams Ob Gyn 2003;101:402-12

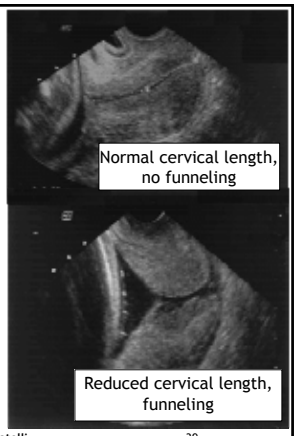
Background (corollary)

Singleton IVF pregnancies: higher risk for spontaneous PTD adjusted for age and parity

Outcome	Number of Studies	IVF n/N	Spontaneous n/N	*P*	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Antepartum						
Delivery <32-33 weeks	4	223/7518	7742/1,105,001	.05		3.10 (2.00, 4.80)
Gestational diabetes	4	57/838	68/1453	.98		2.00 (1.36, 2.99)
Malpresentation	7	302/4658	296/5430	.05		1.03 (0.74, 1.44)
Placenta previa	6	39/1610	21/2382	.37		2.87 (1.54, 5.37)
Preeclampsia	8	233/2256	8149/217,126	.19		1.55 (1.23, 1.95)
Preterm delivery after spontaneous labor	5	182/1770	131/2345	.92		2.09 (1.65, 2.65)
Stillbirth	7	70/5953	2197/239,596	.94		2.55 (1.78, 3.64)
Vaginal bleeding	7	456/2751	6307/216,549	.04		2.52 (1.93, 3.29)

Jackson, *Obstet Gynecol*, 2004, 103(3), 551-63

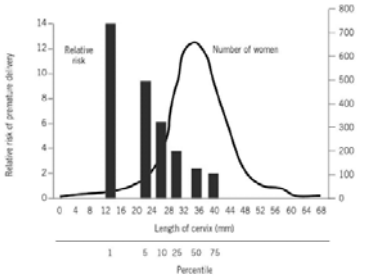




How to measure CL?

- empty bladder
- dorsal lithotomy position
- placed transducer as close as possible to the cervix without pressure, to avoid any deformation or elongation of the cervical canal
- cervical canal identified by the sonolucent endocervical mucosa
- calipers measures the distance between the triangular area of echodensity at the external os and the T-shaped or V-shaped internal os

CL and risk of PTD



Low risk

Iams N Engl J Med 1996;334:567-72

CL: Honest review for singletons

Asymptomatic women: value of CL <25 mm for prediction of PTD <34 w

Weeks at test	pretest prob	posttest prob test +	test -
<20	4.1%	21.2%	3.3%
20-24	4.1%	15.8%	2.7%
>24	4.1%	14.3%	2.6%

Ultrasound Ob Gyn 2003;22:305-22

How about TVS CL as 1st trimester screening for PTD?

- Detection of a short cervix in the late second trimester by means of TVS is a strong predictor of PTD
- Association with other tests (fibronectin)
- The role of this method before 16 weeks' as a screening tool to predict PTD is still controversial

How about TVS CL as screening for PTD in the 1st trimester?

Study 1- prospective study

- 2469 unselected asymptomatic women with singleton pregnancies
- TVS CL measured at 13–15 weeks' gestation
- spontaneous PTD at <37 wks (1.7%) and <34 wks (0.2%)

Conoscenti G UOG 2003

Study 1

No difference between CL in women who delivered at term and those who delivered preterm

Table 2 Length of the cervical canal (in millimeters) at 14 weeks' gestation and its distribution by percentiles in women with term and preterm delivery (PTD). Patients with PTD are stratified into those who delivered between 34 and 37 weeks, and before 34 weeks

	Term delivery	*All cases with PTD < 37 weeks*	*PTD 34–37 weeks*	*PTD < 34 weeks*	*Statistical significance*
n	2427	42	36	6	
Mean cervical length	44	44	45	44	NS*
± 1 SD	5	6	6	7	
Range	23–68	34–60	37–60	34–54	
5th percentile	37	38	38	35	NS*
25th percentile	40	39	40	39	NS*
50th percentile	44	44	44	45	NS*
90th percentile	51	52	52	50	NS*

*Term deliveries versus all cases of PTDs. NS, not significant; PTD, preterm delivery; SD, standard deviation.

How about TVS CL as screening for PTD in the 1st trimester?

Study 2- Prospective study: 183 high risk asymptomatic women

- TVS at 10+0 wks to 13+6 wks
- 20% PD <35wks
- 5% patients had a cervix <25 mm (short cervix) before 14 weeks
- if short cervix prophylactic cerclage performed at 12–14 weeks

In high-risk patients destined to PTD

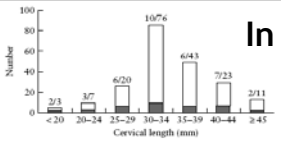
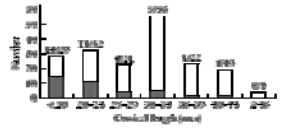


Figure 1 Distribution of total number of patients (total bar heights) and number of patients with preterm delivery (bottom shaded areas) by cervical length at 10 to 13 + 6 weeks (*n* = 183). On top of each bar, the ratio of the number of patients with preterm delivery/total number of patients (for each cervical-length group) is given.

CL <25 mm rarely occurs <14 weeks (10 cases/183)



cervical changes predictive of preterm birth develop mostly after this gestational age

⇨ **test sensitivity 14%**
test specificity 97%
+LR 2.8 (95% CI 1.4-5.6)

Berghella Ob Gyn 2003

How about TVS CL as screening for PTD in the 1st trimester?

Study 3- prospective study, 152 asymptomatic women with singleton pregnancies

- TVS at 10–14 and 20–24 wks
- 10.5% PTD <35 wks (no statistically significant differences in previous history between the group that delivered at term and the preterm group)

Ozdemir I EJOG & Reprod Biol 2007

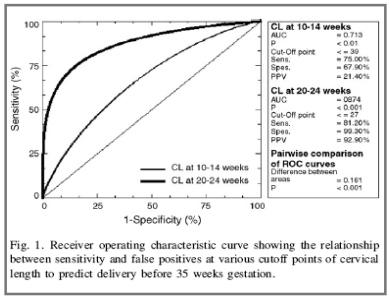


Fig. 1. Receiver operating characteristic curve showing the relationship between sensitivity and false positives at various cutoff points of cervical length to predict delivery before 35 weeks gestation.

Ozdemir I EJOG & Reprod Biol 2007

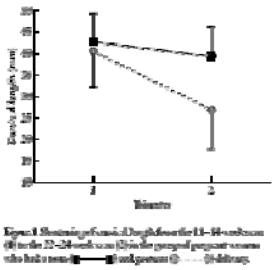
CL measurement better predictor of preterm delivery at 20-24 weeks than at 10-14 weeks

How about sequential change of TVS CL?

Study 4- prospective study, 529 unselected women with singleton pregnancies

- TVS at 11–14 wks and 22–24 wks
- 4.3% PTD <37 wks

Carvalho MHB UOG 2003



- CL at 11–14 wks not significantly different between group delivered at term vs preterm
- CL at the 22–24 wks is significantly shorter in the PTD group than in that delivered at term

Carvalho MHB UOG 2003

The shortening is more rapid in pregnant women who deliver prematurely and have a history of previous PTD

How about sequential change of TVS CL?

Study 5- prospective study, 605 singleton gestation of high risk women

- 2601 TVS CL between 12 and 32 wks
- PTD <35 wks (17.7%), <32 wks (10.6%), <28 wks (6.7%)
- risk of PTD increases as the CL declines and as the gestational age decreases

Berghella V Ob Gyn 2007

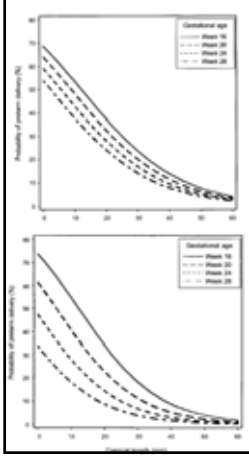
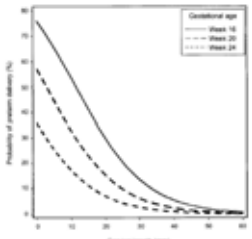


Fig. b



Risk of preterm birth decreased by 6% for each additional mm of CL (OR 0.94, 95% CI 0.92-0.95) by 5% for each additional week of pregnancy (OR 0.95, 95% CI 0.92- 0.98)

Probability of delivery before 35, 32, 28 week respectively, by cervical length (mm) and week of pregnancy

Conclusions 2 Cervical length

- Before 15 weeks, cervical length is usually normal and at times artificially long (the lower uterine segment cannot be distinguished from the cervical canal).
- Short cervix in high risk women is relevant but present only in 5% of women destined to PB (i.e. multiple prior second trimester losses or large cold knife cones)
- Use of combinations of tests (fibronectin not applicable) not explored