

The Role of Cervical Length Measurement in the First Trimester of Pregnancy for the Prediction of Preterm Delivery

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ABSTRACT Preterm delivery (PTD) is the leading cause of perinatal mortality and long-term morbidity. Because of the implications of PTD, we underwent a meta-analysis of current literature to assess the relationship between cervical length and the risk of PTD.

KEY WORDS preterm delivery, pregnancy, cervical length

Introduction

Preterm delivery (PTD) defined by World Health Organization as birth before the completion of 37 weeks' of gestation, is the leading cause of perinatal mortality and long-term morbidity [1-3]. However the relationship between neonatal mortality and morbidity with gestational age (GA) is not linear and decreases significantly after 32-34 weeks, reaching results similar to term newborns [4-5]. The incidence of PTD in developed countries is reported around 5-10% [6-10]. Reports from USA suggest that the incidence of PTD increased by at least 33% during the last 20 years [11-12]. This is primarily due to an increase of late PTD (34-36⁺⁶ weeks), while the incidence of PTD before 34 weeks of gestation remains stable since 1990, at around 2.9-3.6% [3,13]. For the year 2005 the incidence of PTD was calculated as 9.6%, which corresponds to 12.9 million births worldwide [14].

PTD accounts for 75% of perinatal mortality – 60% is due to infants born before 32 weeks – and more than half of the long term morbidity and neurological disabilities in newborns [11,15-16]. In 2001, PTD surpassed birth defects as the leading cause of neonatal mortality [17]. In 2005 the cost of PTD in USA was more than \$26.2 billion [15]. It is of great interest in obstetrics to find methods in order to primarily predict PTD and eventually prevent it. Transvaginal ultrasound (TVU) measurement of the uterine cervical length (CL) at 20-24 weeks of gestation has been reported so far as the best method for the prediction of PTD [18-21]. The shorter the CL in mid-trimester, the higher the risk of PTD [18,20,22-26]. What is more, the use of vaginal progesterone in women that were found to have a short cervix at 20-24 weeks of gestation, appears

to be an effective method of treatment for these women, as some recent studies show that it can reduce the rate of preterm births even by 45% [27-29]. Additionally, recent studies have evaluated the use of cervical pessaries in selected cases, e.g. in women with cervical incompetence, and showed that it may prevent preterm delivery [30-32]. The development of such methods that appear to decrease the risk of preterm delivery promotes the need of earlier detection of women at risk for preterm delivery, even before 14 weeks of gestation and evaluate whether application of these methods to these at risk patients earlier in pregnancy, can have even better results and decrease further the rate of PTD.

Cervical length measurement during the first trimester of pregnancy

Most studies suggest that CL measurement at 11-14 weeks of gestation does not appear to be predictive of PTD (Table-1) [33-35, 40-41]. These results were verified by a recent study from our centre, with a low risk population which consisted of 1511 women, with a viable singleton pregnancy. Measurement of CL at 11-14 weeks of pregnancy did not show any predictive value for PTD before 35 weeks, or even before 32 weeks of gestation and although statistically it appeared to have a predictive value for PTD before 37 weeks, the sensitivity and specificity were very low (AUC=0.6, 95% CI: 0.54-0.66, p=0.001). It was also noticed that cervical length less than 25 mm is a rare finding before 14 weeks [35].

Before 14 weeks, almost all women including those at high risk for PTD or those who will eventually have an early PTD, usually have CL more than 25 mm [22,34]. In a big study from

Greece with more than 1000 women, only one woman was identified with CL less than 25 mm, who had one previous term delivery, no history of cervical treatment and in the current pregnancy the patient delivered at term. Even for women who underwent cervical cerclage because of previous obstetric history, none of them had CL less than 25 mm. Guzman *et al.* studied 469 high risk women for PTD, and found only two with short CL at 15 weeks. Both women had a history of previous second trimester loss [39]. In a recent study from our centre there were included 19 women with previous history of late miscarriage (at 16-23 weeks) and 14 with previous history of very PTD (24-32 weeks). None of these women

had short CL and their average CL was 39.9 mm (range 31-50 mm, median=40 mm) [35]. According to Berghella *et al.* CL less than 25 mm before 15 weeks is seen only in a small percentage (~5%) of women, mainly with history of previous second trimester loss or in women with a history of a large cervical cone biopsy [34]. In a recent study the percentage of women with CL less than 25 mm at 11-14 weeks was 0.09%, possibly due to the fact that the population was low risk, with a low incidence of PTD. The finding that CL is rarely <25 mm before 14 weeks has been verified in different studies [34-35].

Table 1. Studies for prediction of preterm delivery by early ultrasonographic measurement of cervical length

Reference	Year	Study Population	No. (N)	GA at CL (weeks)	CL Cutoff (mm)	Mean CL (mm)		Predictive of PTD
Zorzoli <i>et al.</i> ⁴⁷	1994	Unselected	154	12				No
Hasegawa <i>et al.</i> ⁴⁸	1996	Low Risk	298	8-12	< 30			No
Rosenberg <i>et al.</i> ⁴⁹	1995	Unselected	280	1 st Trimester		37±5.9 36±5.2	Term <25weeks	No
Zalar ⁴²	1998	Unselected	373	11 (11.3±1.9)	< 40 < 30	48.2±8.8 46.7±6.4 49.5±9.8	All Primip Multip	Yes
Naim <i>et al.</i> ⁴⁵	2002	Low Risk	154	< 16	< 30 30-35 35-40 > 40		31 (20%) 59 (38%) 44 (29%) 20 (13%)	Yes
Berghella <i>et al.</i> ³⁴	2003	High Risk	183	10-13 ^{±6}	< 25	33.7±6.9 35.0±6.8	Preterm Term	No
Carvalho <i>et al.</i> ⁴¹	2003	Unselected	529	11-14	< 20	42.4 42.7 40.6	All Term Preterm	No
Conoscenti <i>et al.</i> ³³	2003	Unselected	2469	13-15 ^{±6}		44.2±5.4 44±5 44±6	All Term Preterm	No
Tsikouras <i>et al.</i> ⁴⁶	2007	High Risk	500	9-12	< 30 ≥ 30		216(43%) 284(57%)	Yes
Ozdemir <i>et al.</i> ⁴⁰	2007	Unselected	152	10-14	< 27 < 39	40.9±4.8 38.6±6.3	Term Preterm	No
Antsaklis <i>et al.</i> ³⁵	2009	Unselected	1113	11-14	< 27 < 30	40.6±5.5 40.8±5.5 38.9±5.5	All Term Preterm	No
Greco <i>et al.</i> ⁵⁰	2011	Unselected	1508	11-14	endocx cx-isth endocx cx-isth endocx cx-isth	32.4 45.3 32.5 45.4 27.5 41.4	All All ≥34wks ≥34wks <34 wks <34 wks	Yes
Souka <i>et al.</i> ⁵¹	2011	Unselected	528	11-14	endocx	33 shorter shorter shorter	All <37 wks <34 wks <32 wks	Yes
Greco <i>et al.</i> ⁵²	2012	Unselected	9974	11-14	endocx	32 31 29	Term 34-36 wks <34 wks	Yes

GA: Gestational Age, CL: Cervical Length, No: Number of Patients, PTD: preterm delivery, Endocx: endocervical length, Cx-isth: cervico-isthmus length

The mean CL at first trimester has been calculated in many studies. Antsaklis *et al.* calculated the mean cervical length at 40.8 ±5.5 mm for deliveries ≥37 weeks (1018 women, range: 20-62 mm, 5th percentile = 33 mm) and

38.9 ±5.5 mm for deliveries <37 weeks (94 women, range: 26-54 mm, 5th percentile = 30 mm). These findings were in consistence with Ozdemir *et al.* who studied 152 asymptomatic women and calculated the mean CL at 10-14

weeks as 40.9 ± 4.8 mm and 38.6 ± 6.3 mm, for term and PTD respectively [40]. Conoscenti *et al.* in an unselected population of 2469 women, who underwent CL measurement at 13-15⁺⁶ weeks, found the mean CL to be 44 ± 5 mm for term and 44 ± 6 mm for PTD [33]. There were two differences in the two studies, first the mean GA at examination (14⁺² weeks ± 4 days in Conoscenti *et al.* versus 12⁺¹ weeks ± 2 days in study by Antsaklis *et al.*) and second the rate of PTD (<37 weeks), which was 1.7% (42/2469) for the Italian group versus 8.5% (94/1113) in the Greek group [35], which could explain the discrepancy in the results. Carvalho *et al.* had similar results and these results were also consistent with two previous studies [41-43]. Berghella *et al.* in 183 high risk pregnancies calculated the mean CL as 35.0 ± 6.8 mm and 33.7 ± 6.9 mm for term and PTD respectively [34]. This was a very high risk population compared to the populations of previous studies and that could explain the differences in the measurements.

Most studies had very low risk populations, with a PTD rate <34 weeks of less than 1.3%. Also, from the Greek study 11 women who underwent cervical cerclage, due to previous obstetric history and seven women who had a late miscarriage between 16-23 weeks, were excluded from the study. Especially for the later population cervical length measurement before 14 weeks could be more informative, as changes in the cervix could have started becoming visible.

Measurement of the CL before 14 weeks has not been found to be predictive of PTD [22,33-35]. Only a limited number of studies have shown association between short CL early in pregnancy and PTD [42-45]. In these studies the CL was measured after 15 weeks [44], or the studied population was not homogenous in terms of GA at which the examination was performed [45], or the study population was very high risk [46]. Two studies which compared the CL in first and second trimester did not show any predictive association of the CL at 10-14 weeks for PTD or any statistical difference of the CL between women who delivered at term and preterm [40-41]. An explanation could be that it is difficult to measure the cervix before 14 weeks, as it cannot be easily distinguished from the lower uterine segment, since the gestational sac has not reached a sufficient size to expand the lower part of the uterus [36].

Cervicometry in the first trimester: newer data

Studies have showed that CL at 11-14 weeks does not appear to be predictive of PTD [33-35]. These however are relatively limited studies and has been suggested that further research should be undertaken to assess if ultrasound examination before 14 weeks can indeed provide information about the individual risk of PTD and if at that GA the cervix of women who will eventually deliver prematurely will have any differences compared to women who will deliver at term. However Greco *et al.* proposed a new method for the measurement of cervical length in the first trimester of pregnancy, making a distinction between the endocervix and the isthmus, which appears as a myometrial thickening between the endocervix and the gestational sac. They suggested that what should be measured is first the linear distance between the two ends of the glandular area around the endocervical canal (endocervical length) and second the shortest distance between the glandular area and the gestational sac (isthmus length), distinguishing between the endocervix and the isthmus (Fig. 1a & 1b).



Fig. 1a & 1b: Transvaginal ultrasound pictures illustrating (1a) the cervico-isthmus complex and (1b) the measurement of the length of the endocervix (A to B) and the isthmus (C to D).

They studied 1492 women and they found that the endocervical length at 11-14 weeks is shorter in pregnancies resulting in spontaneous delivery before 34 weeks than in those delivering after 34

weeks. They also suggested that they found no significant differences in the length of the whole length of the cervico-isthmic complex, between the women who delivered before and after 34 weeks, and that could explain the failure of previous studies to show any predictive value of cervical length measurement in the first trimester [50]. Following this study Souka *et al.* measured with the same method the cervical length in 800 women with singleton pregnancies and showed that cervical length at 11-14 weeks of gestation predicted preterm delivery before 34 weeks (odds ratio, 0.746; 95% confidence interval, 0.649-0.869) and preterm delivery before 32 weeks (odds ratio, 0.734; 95% confidence interval, 0.637-0.912) [51]. A more recent study by Greco *et al.* showed that cervical length at 11-14 weeks of gestation is shorter in women who have

spontaneous preterm delivery than in those women who deliver at term, and by using an algorithm combining maternal characteristics and cervical length about 55% of women who will deliver before 34 weeks can be identified, at a false positive rate of 10% [52]. These studies show some predictive value of the measurement of the endocervical length in the first trimester of pregnancy for preterm delivery, and the results of bigger studies are awaited.

Cervicometry in the first trimester and second trimester

There are only a few studies that have focused on the changes that occur to the cervical length from the first to the second trimester of pregnancy and their predictive value for PTD (Table-2).

Table 2 Studies comparing cervical length at first and second trimester

Reference	Year	Study Population	No. (N)	GA at CL 1 st trimester (weeks)	GA at CL 2 nd trimester (weeks)	Mean CL change (mm)	Predictive of PTD
Carvalho <i>et al.</i>⁴¹	2003	Unselected	529	11-14	22-24	3.4 13.9	Term Preterm Yes
Ozdemir <i>et al.</i>⁴⁰	2007	Unselected	152	10-14	20-24	3.1 10.2	Term Preterm Yes
Antsaklis <i>et al.</i>	2009	Unselected	833	11-14	20-24	3.2 7.3	Term Preterm Yes
Souka <i>et al.</i>⁵¹	2011	Unselected	528	11-14	20-24	2.36 3.53 6.29	All Hx CxS Hx PTD Yes

Hx CxS: history of cervical surgery

Hx PTD: history of preterm delivery

^{*} unpublished data from Antsaklis *et al.*

Carvalho *et al.* studied the cervical length of 529 women both at 11-14 weeks and at 22-24 weeks of gestation and reported that the shortening of the cervical length was more significant in women who eventually delivered preterm (13.9 mm) than those who delivered at term (3.4 mm) and it was an independent predictor of preterm delivery [41]. A few years later Ozdemir *et al.* examined 152 low risk patients at similar gestational ages, 10-14 and 20-24 weeks. The cervical shortening was more prominent in the group that delivered preterm (10.2 mm) compared to that delivered at term (3.21 mm) [40]. In our centre we performed a study with similar design that compared the cervical shortening from 11-14 weeks to 20-24 weeks in 833 low risk women. The cervical shortening was 7.3 mm for the preterm group and significantly higher than that in the term group (3.2 mm) (Antsaklis *et al.* unpublished data). More recently Souka *et al.* in a study with 800 women performed serial ultrasound measurements of the cervix at 11-14 weeks, 16-19 weeks and 20-24 weeks of pregnancy, including maternal characteristics and

history of cervical surgery, showed that women with history of cervical surgery and with a history of preterm delivery had a more significant decrease in the cervical length from first to second trimester and that and that by combining all these parameters a short cervix at 20-24 weeks could be predicted at the 11-14 weeks scan, helping to identify earlier women at risk for preterm delivery [51,53].

Conclusions

The role of cervical length measurement at 11-14 weeks of gestation for the prediction of preterm delivery is not well defined yet. Most studies show that cervical length measurement during the first trimester of pregnancy does not appear to be predictive of PTD. These however are relatively limited studies and newer studies that proposed measuring the endocervical length avoiding the lower uterine segment (isthmic part) show more promising results for the prediction of preterm delivery. Further research should be undertaken to assess if ultrasound examination before 14 weeks can indeed provide information about the

individual risk of PTD and if at that GA the cervix of women who will eventually deliver prematurely will have any differences compared to women who will deliver at term. Shifting the prediction of preterm delivery and the identification of high risk women for PTD before 14 weeks of pregnancy, is of great interest in obstetrics as it could give the opportunity for early intervention and that hopefully could be a significant step for the development of an effective strategy for the prevention of the greatest obstetric complications, preterm delivery.

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