Is mid-gestational cervical length measurement as sensitive prediction factor of preterm delivery in IVF as in spontaneous singleton pregnancies?

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Abstract

OBJECTIVES: To verify the relation between pregnancy duration and cervical length (CL) at 22–24 wks of spontaneous and IVF singleton gestations and to assess its predictive value for preterm delivery (< 37 wks).

MATERIAL & METHODS: CL at 22–24 wks was performed according to FMF recommendations in 344 women who conceived spontaneously and in 107 IVF singleton pregnancies. The results of CL in both groups were divided into subgroups: ≤ 29 mm, 30–34 mm; 35–39 mm; 40–44 mm; 45–49 mm and ≥ 50 mm. They were subsequently correlated with mean durations of gestation within subgroups and parameters of accuracy were calculated. Correlation and regression analysis was performed.

RESULTS: The average age of women in both groups was 28.1 y.o. (SD=4.2 years) and 33.4 y.o. (SD=4.1 years), respectively. The mean gestation age at delivery was 38.9 wks (SD=2.1 wks) vs. 37.9 wks (SD=2.3 wks) and the rate of prematurity equaled 7% vs. 15%, respectively. Regardless the method of conception there is a positive correlation between the CL and the duration of gestation. The regression analysis showed that the significant increase in pregnancy duration was correlated with CL ≥ 35 mm (correlation coefficient greater for spontaneous vs. IVF: r_{xy}=0.418 vs r_{xy}=0.341; p<0.001). All CL parameters of accuracy were better for spontaneous in comparison to IVF pregnancies.

CONCLUSIONS: IVF singleton pregnancy carries additional risk factors for preterm delivery. Therefore mid-gestational cervical length is less sensitive predictor than in spontaneous singleton gestations.

ORIGINAL ARTICLE

INTRODUCTION

Preterm delivery is one of the most important issues in perinatology, especially in terms of perinatal mortality and long-term morbidity. Each year around 4 million neonates die before they reach first month of age. In developed countries half of these cases are related to preterm delivery (Bibby & Stewart 2004). During last 5 decades the preterm delivery rate has remained almost the same, despite spectacular progress in medicine. Moreover, the rate of prematurity is even higher in highly developed countries. There are two possible reasons to explain this situation: the lack of effective screening test for preterm delivery to identify high risk patients, and no effective intervention method (Fetal Medicine Foundation 2009; Celik *et al.* 2008; Wielgos & Wegrzyn 2009; Berghella *et al.* 2009).

The rate of preterm delivery before 37 completed gestational weeks is around 7–11%, out of which 1–4% takes place before 34 wks. In Poland, depending on the region of the country, preterm delivery rates range from 4.5 to 12%. According to Polish Gynecological Society the rate of prematurity in 2004 equaled 6.4% (Rekomendacje PTG 2009). Owing to improvements in neonatal care, the risk of fetal death and handicap is mainly increased in very preterm deliveries (<33 wks), so they cannot really be compared to so-called mild preterm deliveries between 34–36 wks.

Among women delivering preterm two groups may be distinguished:

1. Patients with poor obstetric history (high risk of preterm delivery population) contribute to around 15% of all preterm deliveries (only about 3% of all pregnant women). In these patients the risk of subsequent preterm delivery is inversely related to the gestational age at previous preterm delivery.
2. Nulliparous women or women with no history of preterm delivery contribute to 85% of preterm deliveries. This is a low risk population (around 97% of all pregnant women).

The strategy for reducing the rate of prematurity should not be focused on high-risk women, because it would have a very small impact on the overall preterm delivery rate and such strategy would not be successful. All efforts should be concentrated on developing an effective screening test for preterm delivery in patients from the low risk group. Many clinical trials from the last 2 decades demonstrate that among all analyzed parameters and patients' characteristics the mid-gestational cervical length measurement has so far been the best and independent prediction factor of preterm delivery.

OBJECTIVES

The objective of the study was to assess the distribution of second trimester cervical length (CL) in the population of spontaneous singleton pregnancies and singleton pregnancies after in vitro fertilization (IVF) and to verify if CL is as good prediction factor of preterm delivery in IVF as it is in spontaneous pregnancies.

MATERIAL AND METHODS

The material of the study consisted of women in singleton pregnancies attending a second trimester scan at 22–24 weeks of gestation, who consented for a transvaginal cervical length measurement. All measurements were performed according to Fetal Medicine Foundation (FMF) recommendations in order to be repeatable and reproducible. A patient with empty bladder lay in the dorsal lithotomy position, ultrasound probe was introduced in the anterior vaginal fornix with no pressure, sagittal view of the cervix was obtained and the linear distance between external and internal os measured (Fetal Medicine Foundation, 2009). All the examinations were performed at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, between December 2007 and December 2010.

A total of 451 Caucasian women in singleton pregnancies and no obstetric risk factors of preterm delivery were included in the study. The study group was divided into 2 subgroups: 344 spontaneous singleton pregnancies and 107 IVF singleton pregnancies. IVF pregnancies were separated because of their specificity and numerous reports regarding increased risk of preterm delivery in this group. Patients with high risk of preterm delivery, poor obstetric history, congenital fetal anomaly, with a pessary / cerclage *in situ* or premature rupture of membranes at 22–24 weeks of gestation were initially excluded from the study. Additional patients' characteristics, such as age, pre-pregnancy body mass index (BMI) and socio-demographic data were taken into account.

The analyzed variables included: CL at 22–24 weeks of gestation, duration of pregnancy, rates of premature deliveries <33 and <37 wks in both subgroups. Statistical analysis was performed with the use of Statistica 9.1 (Mann-Whitney test, Student T-test) with $p<0.05$ considered significant. CL was additionally correlated with the duration of pregnancy, patients' BMI and maternal age in both spontaneous and IVF pregnancies. Statistical dependence between those variables was measured with the use of Spearman's rank and Pearson's correlation coefficients.

RESULTS

Complete data on 451 women was collected. The mean age of IVF patients was 33.4 y.o. (SD = 4.1, range 25–44 years) and 28.1 (SD = 4.2, range 17–42 years) in spontaneous pregnancies ($p<0.001$). 84.7% of women in IVF group and 34.9% in spontaneous pregnancy group were > 30 y.o. ($p<0.001$). There was no correlation between age and CL in both groups (r=–0.05 for IVF and r=–0.15 for spontaneous pregnancies). Most

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women in both groups came from urban areas. The majority of IVF patients had higher education (69.1% vs. 51.7% in spontaneous pregnancies; $p<0.02$). There were no significant differences between subgroups regarding obstetric history, as the majority of analyzed women were primigravidas (88.5% vs. 91.7% respectively).

There was no correlation between pre-pregnancy BMI and CL in both groups. Spearman's correlation coefficients were: r=–0.17 for IVF and r=0.08 for spontaneous pregnancies ($p>0.05$).

The mean duration of pregnancy was 37.9 wks (SD = 2.3 wks) in IVF and 38.9 wks (SD = 2.1 wks) in spontaneous pregnancies. Although the difference of one week does not seem clinically important, it was highly significant ($p<0.001$). The majority of women in IVF (85%) and spontaneous pregnancy (93%) groups delivered between 37–41 wks. Preterm deliveries < 37 wks contributed to 15% and 7% of all deliveries, respectively ($p<0.05$). Rates of deliveries < 33 wks of gestation equaled 5.6% in IVF and 2.2% in spontaneous pregnancies ($p<0.05$). The results of CL in both groups were divided into subgroups: ≤ 29mm (too few patients with CL below 25 mm); 30–34 mm; 35–39 mm; 40–44 mm; 45–49 mm and ≥ 50 mm. Subsequently they were correlated with mean durations of gestation within certain subgroups. The relation between both variables is positive, regardless of the method of conception: the longer the CL, the longer the duration of gestation. The empiric regression analysis (Figure 1) showed that the significant increase in pregnancy duration was correlated with CL ≥ 35mm (correlation coefficient greater for spontaneous vs. IVF: $r_{xy} = 0.418$ vs. $r_{xy} = 0.341$; $p<0.001$). When CL at mid-gestation was ≥ 35 mm, duration of pregnancy was at least 2–3 weeks longer (mean duration if CL < 35 mm: 36.5 wks in IVF, 36.6 wks in spontaneous; mean duration if CL ≥ 35 mm: 38.2 wks in IVF, 39.3 wks in spontaneous pregnancies).

Finally CL parameters of accuracy were calculated for both groups and they were better for spontaneous in comparison to IVF pregnancies (Table 1).

Tab. 1. Cervical length measurement parameters of accuracy for preterm delivery < 37 wks.

Parameter of accuracy	IVF pregnancies	Spontaneous pregnancies
Sensitivity	0.500	0.750
Specificity	0.889	0.917
False negative results	0.500	0.250
False positive results	0.110	0.083
Positive predictive value	0.333	0.316
Negative predictive value	0.941	0.986

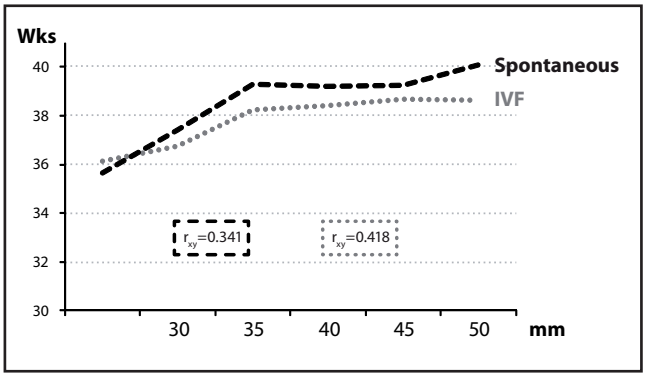

Fig. 1. Empiric regression of pregnancy duration (wks – weeks of gestation) in relation to cervical length measurement (mm).

DISCUSSION

Prolonged or unnecessary tocolysis and unjustified administration of steroids should be avoided. Therefore, it is of great importance to find a screening tool, which would enable us to identify women at high risk of real preterm delivery and to treat them according to current standards.

As for now mid-gestational transvaginal cervical length measurement is the most effective and independent prediction factor for preterm delivery. The proper cut-off value to select patients of highest risk of preterm delivery seems to be the only controversy. Various cut-off values were used in published studies (Crane & Hutchens 2008a). The cut-off value of < 35 mm used in our study is greater than reported by other authors. Small number of women with very short cervix at mid-gestation in the analyzed population could be responsible. In addition IVF and spontaneous pregnancies were separated in order to verify if CL is equally good predictor of preterm delivery in both groups. The majority of publications on IVF pregnancies suggest that they are at risk of poor obstetric outcome, especially preterm delivery. Dhont *et al.* (1999) reported that the rate of preterm delivery in IVF pregnancies was 11.3% vs. 4.9% in spontaneous. Other authors also published similar results, even after adjusting for age, weight, parity, smoking habits and ethnicity (Tallo *et al.* 1995; Koudstaal *et al.* 2000). Systemic reviews and meta-analysis also point out similar results and mention that the risk of very preterm delivery in IVF patients is also higher than in spontaneous pregnancies (1.3–2.1% vs. 0.3–2.9%, respectively) (Helmerhorst *et al.* 2004; Jackson *et al.* 2004). However, none of the authors has so far explained the reason for such findings. We wanted to find out if in IVF and spontaneous pregnancies CL is different at mid-gestation, since no such information was available in the literature. CL has only been analyzed as a prediction factor in general population.

The only available Cochrane database review (Berghella *et al.* 2009) on ultrasound cervical assessment for preventing preterm delivery identified 12 trials from years 1966–2008. Unfortunately, only 5 of them fulfilled the inclusion criteria for the meta-analysis (a total

of 507 patients). They concluded that: the shorter the cervix, the higher the risk of preterm delivery (Grimes-Dennis & Berghella 2007) and the earlier in pregnancy the cervix shortens, the higher the risk of preterm delivery (Berghella *et al.* 2007). The above conclusions were confirmed in all screened populations (also in this study), both with and without risk factors for preterm delivery in the patients' history. Nevertheless, sensitivity and specificity of CL vary in relation to the cut-off value used (15 or 25 mm) and number of preterm deliveries in analyzed populations (Alfirevic *et al.* 2007; Carlan *et al.* 1997; Ness *et al.* 2007; Palacio *et al.* 2006). Unfortunately, no study on asymptomatic low risk patients was included.

Cochrane meta-analysis concluded that there was insufficient evidence to recommend routine CL screening of asymptomatic or symptomatic pregnant women. In the above research the studied subgroups consisted mainly of asymptomatic women with low risk of preterm delivery with regard to obstetric history – according to other results the cut-off value of 35mm seems to be overestimated. However, our data confirm that the results in asymptomatic low risk populations are not satisfactory.

Alfirevic *et al.* claimed that CL may help to decrease the number of patients receiving inappropriate treatment. Thus, using the cut-off value of 15 mm was defined as a preventive measure allowing avoiding unnecessary tocolysis and steroids administration (Alfirevic *et al.* 2007).

Fonseca *et al.* studied efficacy of vaginal progesterone administration in prevention of preterm delivery. A great number of patients (24 620 pregnant women) without symptoms of preterm delivery was included in the study. Only 1.67% of the above population consisted of women with CL of 15 mm or less. These results support the lack of evident conclusions from our study, as a result of extremely low number of patients with very short cervix.

Multivariate regression analysis showed that risk factors for preterm delivery are: CL, history of preterm delivery and episodes of bleeding during the current pregnancy. The impact of other patients' characteristics, such as race, age, BMI or smoking habits is conflicting (Crane & Hutchens 2008b). In this study no significant correlation was found between CL and maternal age or BMI.

Positive history does not always lead to preterm delivery in the next pregnancy. In these patients CL measurement at 22–24 wks is suggested as a routine examination, providing information required for taking the decision regarding therapeutic intervention. Two large studies by To *et al.* (2006) (39 284 women) and Celik *et al.* (2008) (58 807 women) found that the most effective screening for preterm delivery is provided by measuring cervical length at 20+0–24+6 wks and patient's history.

In our study patients did not have any risk factors for preterm delivery (except for IVF), but our results are not easy for interpretation. It is mainly due to the low number of patients included in the study and therefore few with very short cervix. However, despite the similar cervical length measurement distribution in IVF and in spontaneous singleton pregnancies, CL does not seem equally useful in the IVF group.

It is obvious that no screening test will identify all women in whom preterm delivery will occur. It is a result of the nature of the test, which provides data only about the risk of the incident, not about the diagnosis. Another problem is to distinguish between the real and false preterm delivery and to make a proper decision about administration of tocolytics and steroids.

CONCLUSIONS

Singleton IVF pregnancies carry additional, yet unknown, risk factors of preterm delivery, therefore mid-gestational cervical length measurements are not as sensitive prediction factor as for spontaneous singleton gestations. It is also worth remembering that no available screening tool so far can predict iatrogenic preterm delivery in any population.

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