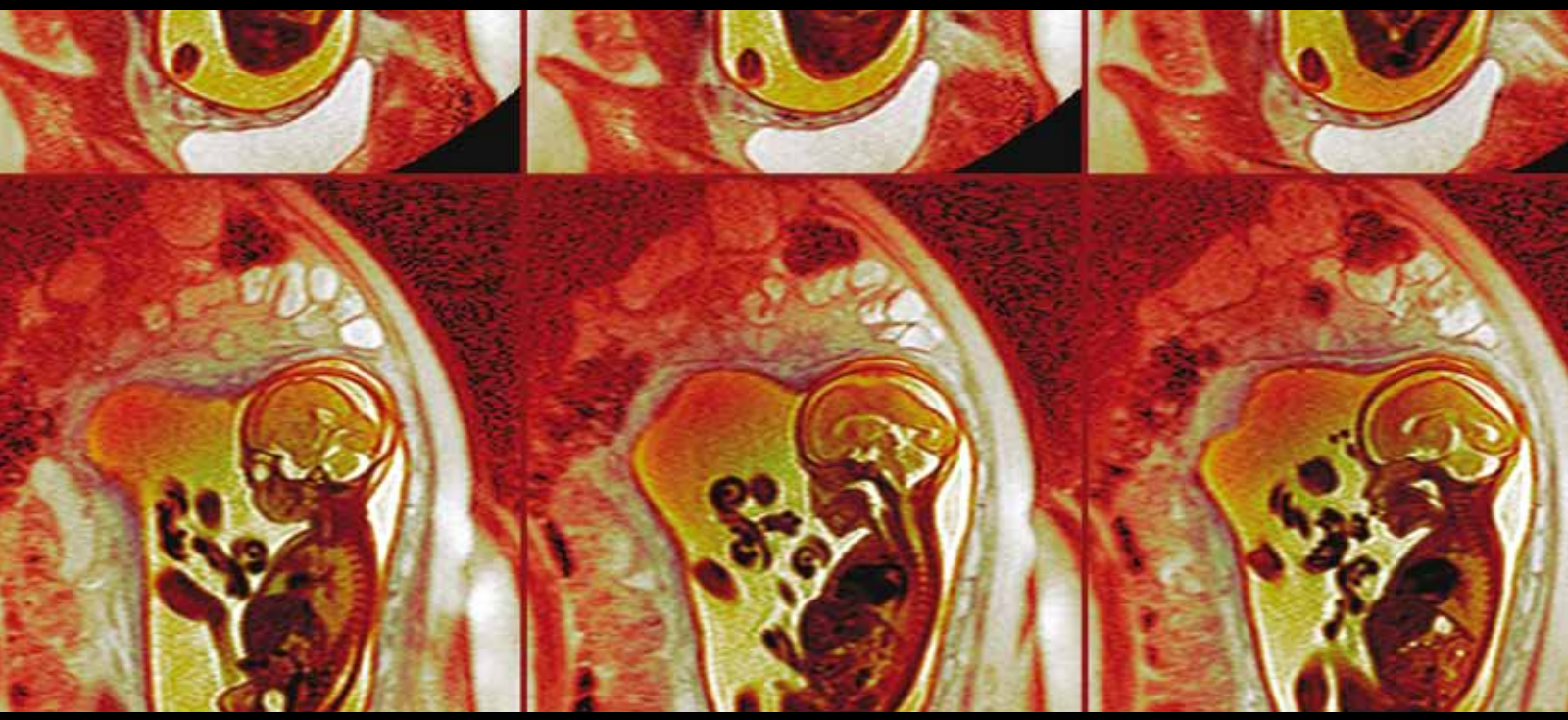
Journal of Pregnancy

Prevention and Management of Preterm Birth

Guest Editors: Yves Jacquemyn, Ronnie Lamont, Jérôme Cornette, and Hanns Helmer



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Contents

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 610364, 1 page
doi:10.1155/2012/610364

Editorial

Prevention and Management of Preterm Birth

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Received 19 December 2011; Accepted 19 December 2011

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Prevention and treatment of preterm delivery is not one of the success stories of modern medicine, preterm birth constitutes the major determinant of perinatal mortality and morbidity, and the long-term results of being born too early often lead to a shorter, less healthy life and a more difficult school and professional career. Different methods have been introduced to predict the advent of preterm labour in asymptomatic women, including fetal fibronectin and transvaginal ultrasound cervical length measurement. R. Arisoy and M. Yayla present data on the evaluation of the cervix in asymptomatic singleton pregnancies; they also address the most frustrating issue: what measures to take once a short cervix has been detected. They restrict their study to singleton pregnancies; although both cervical length and fetal fibronectin are good predictors of preterm delivery in twins, no intervention has proven useful in twins: vaginal progesteron makes no difference and cerclage even worsens the outcome.

Possibilities for real primary prevention are rare and include treatment of asymptomatic bacteriuria and periodontal disease. O. Huck et al. elaborate this last issue and present an excellent overview on both epidemiologic and pathophysiologic data. Another method proposed for primary prevention of preterm birth is the use of progesteron, including vaginal progesteron and systemic 17-hydroxyprogesterone caproate. Starting progesterone treatment can be based not only on cervical length or vaginal fibronectin but also on past obstetrical history. C. E. Ransom et al. comment on the use of 17-hydroxyprogesterone caproate and the influence of obstetric history.

Some newer methods are on the border of being introduced to clinical practice; one such candidate is near-infrared spectroscopy. K. M. Power and colleagues present the use of near-infrared spectroscopy of amniotic fluid to assess preterm delivery.

Once preterm labour has been established, tocolytics are (all too) often used, and what their exact place in treatment is remains open for discussion. Hubinont and F. Debieve present a concise update on tocolysis. In case preterm delivery seems unavoidable, the optimal mode of fetal monitoring and the mode of delivery have to be chosen. Fetal heart rate monitoring in the preterm period constitutes a special challenge and is further commented by K. Afors and E. Chandraharan, while S. R. Bhatta and C. R. Keriakos discuss the optimal way of delivering the preterm baby in vertex position.

As the articles in this issue demonstrate, preterm labour and delivery constitute one of the major challenges of obstetrics in the 21st century.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 201628, 10 pages
doi:10.1155/2012/201628

Review Article

Transvaginal Sonographic Evaluation of the Cervix in Asymptomatic Singleton Pregnancy and Management Options in Short Cervix

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Received 27 March 2011; Accepted 2 November 2011

Academic Editor: Yves Jacquemyn

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Preterm delivery (PTD), defined as birth before 37 completed weeks of gestation, is the leading cause of perinatal morbidity and mortality. Evaluation of the cervical morphology and biometry with transvaginal ultrasonography at 16–24 weeks of gestation is a useful tool to predict the risk of preterm birth in low- and high-risk singleton pregnancies. For instance, a sonographic cervical length (CL) > 30 mm and present cervical gland area have a 96-97% negative predictive value for preterm delivery at <37 weeks. Available evidence supports the use of progesterone to women with cervical length ≤25 mm, irrespective of other risk factors. In women with prior spontaneous PTD with asymptomatic cervical shortening (CL ≤ 25 mm), prophylactic cerclage procedure must be performed and weekly to every two weeks follow-up is essential. This article reviews the evidence in support of the clinical introduction of transvaginal sonography for both the prediction and management of spontaneous preterm labour.

1. Introduction

Preterm delivery occurs in 5–13% of pregnancies before 37 weeks' gestation. Preterm delivery is a major cause of perinatal morbidity and mortality [1–7]. Most of the damage and death cases occur in infants delivered before 34 weeks. The incidence of early preterm delivery (<34 gestational weeks') is 1–3.6% [1, 2]. Preterm delivery is associated with a high prevalence of severe neurological deficits and developmental disabilities and is a leading cause of infant and neonatal mortality. Preterm neonates are at increased risk of developing respiratory distress syndrome, bronchopulmonary dysplasia, sepsis, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, and disorders related to gestational age at birth [8, 9].

Risk factors for preterm delivery include demographic characteristics, behavioral factors, and aspects of obstetric history such as previous preterm birth. Demographic factors for preterm labor include black race, extremes of maternal age (<18 or >35), low socioeconomic status, and low prepregnancy weight. Preterm labor and birth can be associated with stressful life situations (e.g., domestic violence, close family death, work and home environment) either indirectly by associated risk behaviors or directly by mechanisms not completely understood. Many risk factors may manifest in the same gravida [1–3, 10].

The exact mechanism of preterm labor is largely unknown but is believed to include decidual hemorrhage (e.g., abruption, mechanical factors such as uterine overdistension from multiple gestation or polyhydramnios), cervical incompetence (e.g., cone biopsy), müllerian duct abnormalities, fibroid uterus, cervical inflammation (e.g., resulting from bacterial vaginosis, trichomonas), maternal inflammation and fever (e.g., urinary tract infection), hormonal changes (e.g., mediated by maternal or fetal stress), and uteroplacental insufficiency (e.g., hypertension, insulin-dependent diabetes, drug abuse, smoking, alcohol consumption). Each of these underlying causes can initiate the cascade of events that ultimately lead to uterine activity and cervical dilation. Thus, a reduction in the spontaneous PTD rate may require

not only accurate identification of patients at risk for preterm delivery but also effective treatment strategies aimed at correcting the underlying causes of preterm labor [1–3, 10–16].

Methods used for predicting preterm birth include risk scoring system, assessments of salivary estriol, fetal fibronectin (FFN), maternal serum alpha fetoprotein (MS-AFP), cervicovaginal intracellular adhesion molecule-1 (ICAM-1), phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1), cervicovaginal beta-human chorionic gonadotropin (β-hCG), and the cervical morphology and biometry. While hospital tocodynamometry has been effective for monitoring uterine contractions to evaluate preterm labor, home uterine activity monitoring (HUAM) has not been proven valuable in detecting or preventing preterm birth and is not currently recommended for use [17, 18].

2. Biomarkers of Preterm Birth

The most commonly used and most predictive method for preterm birth is fetal fibronectin. Fetal fibronectin (fFN) is a glycoprotein produced by fetal membranes and trophoblasts which form a biological glue that adheres the fetal membranes and placenta to the decidua. Before approximately 20 gestational weeks it is normally found (4%) in secretions of the cervix and vagina. Thereafter it is a pathological finding and a marker of choriodecidual disruption [19–21]. Initially, Lockwood et al. reported that the presence of cervicovaginal fetal fibronectin in the second and third trimesters of pregnancy identifies a subgroup of women who are at high risk for preterm delivery. They showed that fFN had a sensitivity of 81.7% and specificity of 82.5% for detecting PTD at 37 weeks of gestation in asymptomatic patients [19]. The systematic review by Honest et al. demonstrated that in asymptomatic women the best summary likelihood ratio for positive fFN results was 4.01 (95% confidence interval 2.93 to 5.49) for predicting birth before 34 weeks' gestation, with corresponding summary likelihood ratio for negative fFN results of 0.78 (0.72 to 0.84). Among symptomatic women the best summary likelihood ratio for positive results for fFN was 5.42 (4.36 to 6.74) for predicting birth within 7–10 days of testing, with corresponding ratio for negative fFN results of 0.25 (0.20 to 0.31) [22].

Recently, cervical or vaginal fetal fibronectin is the most powerful biochemical prediction marker of SPTD due to the high negative predictive values [23, 24]. Deplange et al. investigated a sequential test with fetal fibronectin detection after ultrasound measurement of cervical length to predict preterm delivery in women with preterm labor. They reported that the sensitivity, specificity, and positive and negative predictive values of fetal fibronectin positiveness were 75, 71, 17, and 97% for delivery within 14 days; those of cervical length inferior or equal to 20 mm were 75, 52, 21, and 92% for delivery before 34 weeks. The efficiency of the sequential test was similar with excellent negative predictive value: sensitivity, specificity, and positive and negative predictive values of 75, 63, 26, and 93.5% for prediction of preterm delivery before 34 entire weeks. The use of this sequential test could have avoided 37% of fibronectin tests [25].

The maternal salivary E3 level seems to correlate well with the serum level and it has been shown that elevated maternal serum E3 levels are associated with increased risk of preterm birth in asymptomatic and symptomatic women presenting for symptoms of preterm labor [26]. It also has low sensitivity and is currently mainly used in clinical settings due to its negative predictive value (i.e., women who test negative are at very low risk of preterm birth and no interventions are necessary) [17, 27]. This test is thus currently more useful for research than for clinical practice [27].

Previous research has showed an association with elevated AFP and adverse pregnancy outcomes, including spontaneous preterm birth. The premature delivery screening can be used at the beginning of the 2nd trimester. Cut-off value of 1.8 MoM for marking the higher-risk group was used for marking the high-risk group. Women with equal or higher values of AFP were 3.8 times more likely to have premature delivery than those with lower AFP values (95% CI: 2.2; 6.3). Sensitivity of 25% and specificity of 92% were proven [28]. At a patient-level meta-analysis of 24 studies by Yuan et al., there was no association with preterm birth (OR = 1.80, 95% CI: 0.92–2.68) at women in whom AFP was elevated in isolation. Their findings suggest that maternal AFP levels are strongly related to preterm birth, but only in the context of other abnormal pregnancy markers [29].

Marvin et al. reported that measurement of sICAM-1 in cervicovaginal fluid has potential as a predictor of preterm delivery in women with symptoms of preterm labor. Elevated sICAM-1 concentrations predicted short intervals to delivery (area under receiver operator characteristic (ROC) curves, 0.70–0.72 for delivery within 3, 7, and 10 days), with high specificity. Characteristics for delivery within 3 days at a 3 ng/mL threshold for a positive test were sensitivity of 33.3%, specificity of 98.9%, and positive and negative predictive values of 75.0% and 93.9%, respectively. Predictive ability was independent of and complementary to that of fetal fibronectin [30]. Kwon et al. showed that ICAM-1 gene K469E polymorphism may be a candidate region and useful predictor of susceptibility to PTD [31].

The recent studies showed that a new cervicovaginal test to detect phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) may improve the accuracy of predicting preterm delivery. The phIGFBP-1 is mainly secreted by maternal decidual cells and may be an indicator of tissue damage of the choriodecidual interface. In the first trimester, 24.5% of women, and in the mid-second trimester, 20.2% of women, had an elevated cervical fluid phIGFBP-1 level [32, 33]. Rahkonen et al. investigated an assessment of phIGFBP-1 in predicting preterm delivery in 5180 unselected pregnant women. They found that the rates of spontaneous PTD before 32 and before 37 weeks of gestation were higher in women with an elevated cervical fluid phIGFBP-1 level, compared with women who had cervical phIGFBP-1 of <10 micrograms/L (1.1% versus 0.3% and 5.7% versus 3.2%, resp.). An elevated phIGFBP-1 level in the first trimester was an independent predictor for PTD before 32 and before 37 weeks of gestation, with odds ratios of 3.0 (95% CI 1.3–7.0) and 1.6 (95% CI 1.2–2.3), respectively. Cervical phIGFBP-1 levels of 10 micrograms/L or more in the first

trimester predicted PTD before 32 and before 37 weeks of gestation, with sensitivities of 53.8% and 37.0%, respectively. The negative predictive values were 99.7% and 96.8%. They showed that elevated cervical fluid phIGFBP-1 levels in the first trimester were associated with an increased risk of spontaneous PTD [34].

In another study, Rahkonen et al. investigated that short cervix (<25 mm), positive phIGFBP-1 test, combination of both, and clinician's judgment were all associated with preterm delivery < or = 34 weeks or within 14 days in a total of 246 women between 22 and 34 weeks of gestation. The negative predictive values for delivery < or = 34 weeks were 97.4, 97.6, 97.1, and 98.7%, respectively, and within 14 days 98.7, 99.0, 98.3, and 99.6%, respectively. The corresponding positive LRs for delivery < or = 34 weeks were 6.8, 3.8, 75.0, and 14.9, and within 14 days 9.7, 5.5, 107.3, and 17.1. The negative LRs were 0.6, 0.6, 0.7, and 0.3 and 0.5, 0.3, 0.6, and 0.2. They showed that the rapid phIGFBP-1-test has a high negative predictive value for preterm delivery, comparable to that of ultrasonographic cervical length measurement [35]. Paternoster et al. assessed phIGFBP-1 in cervical secretions and the sonographic measurement of cervical length in 210 symptomatic patients. They found that 26 mm was the best cut-off value for cervical length in terms of predicting preterm delivery (LR+, 3.69; LR−, 0.22), with a sensitivity of 86.4%, specificity of 71.9%, positive predictive value (PPV) of 34.5%, and negative predicting value (NPV) of 96.8%. They also found that the sensitivity, specificity, PPV, and NPV of phIGFBP-1 of a positive phIGFBP-1 test were 52.9%, 89.2%, 48.7%, and 90.8%, respectively, in predicting birth before 37 weeks' gestation with an OR of 9.3 (95% CI, 4.05–21.3), an LR+ of 4.9, and an LR− of 0.5 and that their combination had an NPV of 90%, greater specificity, and a better PPV (64.3%) than either method alone for preterm delivery [36]. Bittar et al. found that measuring cervical length at 22–24 weeks' gestation and phIGFBP-1 at 30 weeks' gestation improved the prediction of preterm delivery over either method used alone [37].

Audibert et al. reported that IGFBP-1 screening did not predict preterm delivery and fFN screening provided the best predictive capacity. A policy of contingent use of testing for fFN after CL measurement or contingent use of CL measurement after fFN screening (depending on available resources) is a promising approach to limit use of resources [38]. Cooley et al. studied the relationship between levels of insulin-like growth factors 1 and 2 (IGF-1, IGF-2) and insulin-like growth factor binding protein 3 (IGFBP-3) in antenatal maternal serum and gestational age at delivery. They reported that there was no significant association between maternal IGF-1 or IGF-2 and preterm birth (PTB). Maternal mean IGFBP-3 levels are significantly reduced in cases complicated by delivery <32 completed weeks [39].

Cervicovaginal beta-hCG measurement in patients with preterm labor may be used as a predictive test. Bagga et al. studied with a group of 100 women with a singleton pregnancy with preterm labour between 26–36 weeks' gestation. Cervicovaginal secretions were collected for HCG assay and cervical length was measured by transvaginal sonography (TVS). These parameters were analysed to predict preterm birth. The preterm delivery rate was 55%; 24% delivered within 48 h and 11% within 7 days of admission. The sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) of cervical length less than or equal to 2.5 cm to predict delivery within 48 h and 7 days of admission were 62.5%, 89.5%, 65.2%, and 88.3% and 60.0%, 96.9%, 91.3%, and 81.8%, respectively; and those of qualitative HCG were 87.5%, 80.3%, 58.3%, and 95.3% and 77.1%, 86.2%, 75%, and 87.5%, respectively. HCG value of > or = 45 mIU/mL was the optimal cut-off, with a sensitivity, specificity, PPV, and NPV for predicting delivery within 48 h and 7 days to be 95.8%, 73.7%, 53.5%, and 98.2% and 85.7%, 80%, 69.8%, and 91.2%, respectively. Combining either qualitative or quantitative HCG assay with cervical length significantly increased the sensitivity and NPV of cervical length alone for prediction of preterm delivery both within 48 h and 7 days. It was concluded that increased cervicovaginal HCG and reduced cervical length predicted an increased risk of preterm delivery in women with preterm labour. Qualitative cervicovaginal HCG assay may be used as a bedside test to predict preterm delivery within 48 h or within 7 days [40].

Adhikari et al. investigated prediction of the risk of preterm birth (<37 weeks) or early preterm birth (<34 weeks) by cervicovaginal HCG and cervical length measured between 24 and 28 weeks of gestation in asymptomatic women at high risk for preterm birth. They reported that to predict delivery <37 weeks, cervical length <2.95 cm had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 75%, 80.1%, 71.4%, and 90.7% respectively, and cervicovaginal HCG > 4.75 mIU/mL had a sensitivity, specificity, PPV, and NPV of 70%, 61.81%, 40%, and 85%, respectively. To predict delivery <34 weeks, cervical length <2.65 cm had a sensitivity, specificity, PPV, and NPV of 50%, 85.50%, 23.08%, and 95.16%, respectively; and cervicovaginal HCG > 14 mIU/mL had a sensitivity, specificity, PPV, and NPV of 83.3%, 85.5%, 33.3%, and 98.3%, respectively. Cervical length was superior to predict delivery <37 weeks, whereas HCG was superior to predict delivery <34 weeks. Their combination was superior to predict preterm birth both <37 weeks or <34 weeks, than either parameter used alone [41].

Combined marker evaluation could be used as a sensitive parameter for identifying women at risk of spontaneous preterm delivery but it is not possible to obtain biomarkers in most of the clinics. Therefore, the evaluation of the cervix with utrasoundography is important.

3. Cervical Assessment by Ultrasonography

Cervix can be evaluated by transabdominal, translabial, and transvaginal ultrasound (TVU). Each technique has its costs and benefits; however, a review of the current literature will show that the transvaginal method of cervical assessment is the most reliable. TVU is objective, reproducible, and acceptable to patients. At the transabdominal approach, the cervix may not be visualised in up to 50% of cases unless the bladder is full, but bladder filling significantly increases the length of the cervix. The transperineal route is limited by

both the inconsistency in correlation between transvaginal and transperineal measurements and the inadequate visualisation of the cervix in up to 25% of cases. Cervical changes such as dilatation of the internal cervical os with funneling (beaking) of the membranes can be easily appreciated by TVU, but not by digital examination [42–44]. The ultrasound images were analyzed to assess changes in the cervix that are associated with spontaneous prematurity and to evaluate ultrasonography as an indicator of the risk of preterm delivery [45].

Before the evaluation of the cervix with transvaginal ultrasonography, first of all, the patient should have an empty bladder and be placed in dorsal lithotomy position. A distended bladder can alter the shape of the cervix and compass the cervical canal in some cases preventing the detection of cervical incompetence [44, 46]. The vaginal probe should be placed in the anterior fornix without pressure. If the probe is pressed too hard against the cervix, it can obscure cervical incompetence. Initial orientation is established by locating the sagittal view of the cervix. The cervical canal should appear as a hypoechoic groove. The junction between amniotic membrane and cervical canal is designated as the internal os. The external os is located at the lower end of the cervix. Cervical length (CL) is defined as the distance between the internal to external os along the endocervical canal (Figure 1). If the cervical canal is curved, the CL can be measured either as the sum of two straight lines that essentially follow the curve or by a straight line between internal and external os. A short CL is usually straight, and the presence of curved cervix generally signifies a CL greater than 25 mm and, therefore, is a reassuring finding [47, 48].

If the cervical canal is closed, CL is probably the only parameter that needs to be measured. If a normal appearing internal os cannot be visualized, the cervix should be assessed further to determine whether funneling (the internal os width is greater than 5 mm) is present (Figure 2). If funneling is present, the shape can be recorded [49, 50]. A continuous process of funneling has been described, going from a normal T shape to Y, then V, and finally a U shape. It appears that U shape is more likely to be associated with PTD, compared with a V-shaped funnel [51, 52].

CL during pregnancy can range from 25 to 70 mm and ultrasound width of the cervical canal ranges from 2 to 4 mm [47, 48, 53, 54]. Percentile values for CL between 17 and 32 weeks of gestation are indicated in Table 1 (unpublished data). Before 14 weeks, it is difficult to distinguish the lower uterine segment from the endocervical canal. Therefore, the measurement of the true cervical length is very difficult before 14 weeks. There is agreement that the best time to examine patients with this method to estimate their preterm birth risk is between 18 and 24 gestational weeks. Several studies reported that the measurement of cervical length in the first trimester is not predictive of preterm delivery [55, 56]. Finally, Greco et al. have recently reported that the endocervical length at 11 to 13 weeks is shorter in pregnancies resulting in spontaneous delivery before 34 weeks than in those delivering after 34 weeks [57].

Many parameters other than CL and presence or absence of a funnel have been studied including funnel width, funnel length, endocervical canal dilation, cervical index (funnel length +1/functional length), anterior and posterior cervical width, cervical angle, cervical canal contour, and cervical gland area (CGA) [58–60].

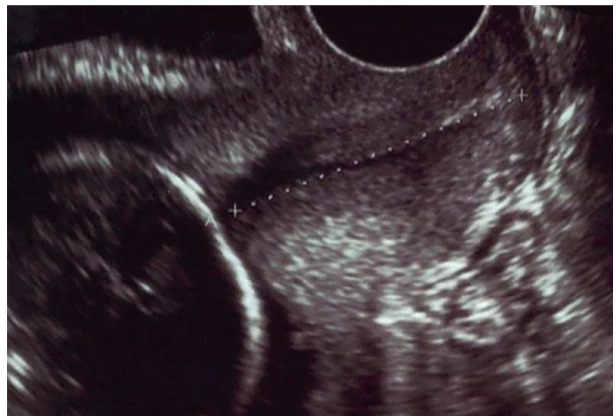

Figure 1: Transvaginal ultrasound image of the uterine cervix.

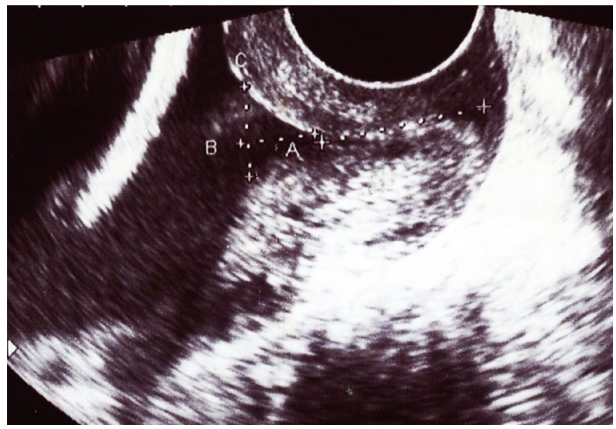

Figure 2: Transvaginal ultrasound image of the cervical funneling.

Table 1: Percentile values for CL between 17 and 32 weeks of gestation.

Group (GW)	Percentiles						
	5	10	25	50	75	90	95
17–20 GW	33,00	34,00	37,00	38,50	41,00	44,00	45,00
21–24 GW	29,00	30,00	34,50	37,00	39,00	41,00	43,00
25–28 GW	27,00	28,00	33,00	35,00	37,00	40,00	41,40
29–32 GW	26,50	28,00	31,00	33,00	36,50	39,00	40,00

4. The Cervical Morphology and Biometry for the Prediction of Preterm Birth

The length of the cervix may be useful in predicting the risk of premature delivery, with a shorter cervix predicting a higher risk. A short CL is a better predictor of early PTD than later PTD [47, 61–63]. In a prospective multicenter study, Iams et al. performed TVS of the cervix in low-risk women

Table 2: Studies of CL measured by transvaginal ultrasonography to predict preterm birth in low-risk women.

Authors	n	GW at testing	Outcome (GW)	Cutoff value (mm)	Sen. (%)	Spec. (%)	PPD (%)	NPD (%)
Tongsong et al. [6]	730	28–30	<37	<35	65.9	62.4	19.4	92.8
Iams et al. [47]	2915	24	<35	≤30	54.0	76.3	9.3	97.4
		24	<35	≤25	37.3	92.2	17.8	97.0
	2531	28	<35	≤30	69.9	68.5	7.0	98.5
		28	<35	≤25	49.4	86.8	11.3	98.0
Fukami et al. [58]	3030	16–19	22–31	≤30	50.0	98.5	8.3	99.9
			32–36	≤30	18.2	98.9	33.3	97.6
Pires et al. [59]	338	21–24	<37	<20	18.0	98.1	40.0	94.8
			<35	<20	27.3	97.9	30.0	97.6
Barber et al. [7]	2351	18–22	<37	<30	39.0	92.0	31.0	94.0

with a singleton pregnancy at 24 weeks ($n = 2915$) and 28 weeks ($n = 2531$) of gestation. At 24 weeks, a cervical length of ≤25 mm had a sensitivity of 37%, a specificity of 92%, a positive predictive value 18%, and a negative predictive value %97 in predicting spontaneous preterm birth at <35 weeks' gestation. The RR of preterm birth before 35 weeks of gestation was about sixfold higher (95% CI: 3.84–9.97) among women whose cervical length was less than 25 mm than that among women with a cervical length above 40 mm [47].

To et al. conducted a population-based prospective multicentre study in 39 284 women with singleton pregnancies attending for routine hospital antenatal care in London, UK. The detection rate of spontaneous delivery before 32 weeks by measuring cervical length was 55%, with 10% false-positive rate [64]. Hibbard et al. measured the CL by TVS at 16–22 weeks in 760 singleton pregnancies in unselected women attending routine antenatal care. Relative risks (95% CI) for spontaneous preterm delivery before 37 weeks were 3.8 (2.6, 5.6), 5.4 (3.3, 9.0), and 6.3 (3.0, 13.0) for the tenth (30 mm), fifth (27 mm), and two and a half (22 mm) percentiles, respectively; RRs for before 35 weeks were 4.5 (2.9, 6.9), 7.5 (4.5, 12.5), and 7.8 (3.6, 16.7). Sensitivity ranged from 13 to 44%, specificity 90–99%, positive predictive value 15–47%, and negative predictive value 80–98% for prediction of preterm birth before 35 weeks [65].

A study of cervical length in low-risk women found an eightfold (95% CI 3–19) increased risk of preterm birth when the cervix was less than 30 mm at 18 to 22 weeks of gestation, but the sensitivity and positive predictive values were low: 19 and 6 percent, respectively [61]. Although low sensitivity and low positive predictive value limit its usefulness, it has high negative predictive values and it can be used in screening of low-risk obstetric populations (Table 2).

A number of studies have assessed the predictive value of TVS CL in women with some of the most important of these risk factors including a prior PTD [50, 66, 67], a history of excisional cervical procedures (cone biopsy, LEEP) [68, 69], mullerian anomaly [70], and two or more voluntary termination [70] (Table 3). In a prospective study of 705 high-risk women, the risk of spontaneous PTB before 35 weeks decreased by approximately 6% for each additional millimeter of CL (OR: 0.94, 95% CI: 0.92–0.95) and by approximately 5% for each additional week of pregnancy during which the CL was measured (OR: 0.95, 95% CI: 0.92–0.98). They conclude that gestational age at which transvaginal ultrasound cervical length is measured significantly affects the calculation of risk of spontaneous preterm birth. The spontaneous preterm birth risk increases as the length of the cervix declines and as the gestational age decreases [71].

Funneling comprising 40–50% of the total cervical length or a persistently shortened cervix (<25–30 mm) has, in several studies, been associated with an increased risk of preterm birth [17, 47, 49, 65]. To et al. measured cervical length among 6334 women with singleton pregnancies at 22–24 weeks and looked for the presence of funneling to evaluate its possible additional risk. Funneling of the internal os was present in about 4% of pregnancies and the prevalence decreased with increasing cervical length from 98% when the length was ≤15 mm to about 25% for lengths of 16–30 mm and less than 1% at lengths of >30 mm. The rate of preterm delivery was 6.9% in those with funneling compared to 0.7% in those without funneling. However, logistic regression analysis demonstrated that funneling did not provide a significant additional contribution to cervical length in the prediction of spontaneous delivery before 33 weeks (OR, for short cervix = 24.9 $P < 0.0001$; OR, for funneling = 1.8, $P = 0.40$) [50].

As an independent finding, funneling does not add appreciably to the risk of early gestational age at delivery associated with a shortened cervical length. So, women with a long cervix and funneling are not at increased risk of preterm delivery [50, 51, 72].

In the past few years publications have also highlighted the importance of another morphological ultrasonographic marker for PTD, named as the cervical gland area (CGA). The CGA is defined as the sonographically hipoechoic or hiperechoic zone surrounding the endocervical canal. If the CGA around the endocervical canal is not detected, it is defined as absent [58, 59].

Fukami et al. reported that the absence of CGA at second trimester ultrasonography appeared to be new and powerful predictor of PTD before 32 weeks gestation [58], similar to that reported by Pires et al. [59] (Table 4). Asakura et al. reported that short CL (<20 mm) with absent CGA represents an independent predictor for PTD. The absence of

Table 3: Studies of CL in high-risk women with spontaneous PTD.

Authors	n	GW at testing	Outcome (GW)	Cutoff value (mm)	Sen. (%)	Spec. (%)	PPD (%)	NPD (%)	RR
Berghella et al. [43]	96	14–30	<35	25.0	59.0	85.0	45.0	91.0	4.8
Owen et al. [48]	183	16–24	<35	25.0	69.0	80.0	55.0	88.0	3.4
Crane and Hutchens [66]	193	24–30	<35	30.0	63.6	77.2	28.0	93.8	—
Adhikari et al. [41]	79	24–28	<37	29.5	75.0	80.1	71.4	90.7	—
			<34	26.5	50.0	85.5	23.1	95.2	—
Berghella et al. [68]	45	16–24	<35	25.0	60.0	69.0	35.0	86.0	2.5
Crane et al. [69]	75	24–30	<37	30.0	70.0	90.8	53.8	95.2	—
Airoldi et al. [70]	64	$14–23^{+6}$	<35	25.0	71.0	91.0	50.0	95.0	13.5
Visintine et al. [72]	131	14–24	<35	25.0	53.0	75.0	48.0	78.0	2.2

Table 4

Authors	n	GW at testing	Test	Outcome (GW)	Sen. (%)	Spec. (%)	PPD (%)	NPD (%)
Fukami et al. [58]	3030	16–19	Absence CGA	22–31	75.0	99.8	54.5	99.9
			CL ≤ 30 mm + Absence CGA	22–31	50.0	99.8	40.0	99.9
			Absence CGA	32–36	2.3	99.7	18.2	97.2
			CL ≤ 30 mm + Absence CGA	32–36	2.3	99.7	20.0	97.2
Pires et al. [59]	338	21–24	Absence CGA	<35	54.5	99.1	66.7	98.5
			Absence CGA	<37	38.1	9.7	88.9	96.0

the CGA as a new marker for the risk of PTD has to be confirmed by further investigations [73].

5. Management Options for Short Cervix

Many interventions have been proposed in an attempt to prevent PTD in women at high risk.

Bed rest and hydration are often recommended in an attempt to prevent PTD in women at high risk, but there is no consistent evidence that they are able to delay delivery [74].

Progesterone's role in the treatment and prevention of preterm birth is still uncertain. A Cochrane meta-analysis from 2005 showed that intramuscular progesterone is associated with a reduction in risk of preterm birth before 37 gestational weeks [75]. Fonseca et al. in a multicenter, randomized trial proposed using daily vaginal micronized progesterone (200 mg) to women with CL 15 mm or less, irrespective of other risk factors. They showed a significant reduction in preterm birth at <34 weeks with intravaginal progesterone in patients treated based on premature cervical shortening as the indication for therapy [76]. O'Brien et al. analyzed 547 randomized patients with a history of preterm birth. They found that the progesterone-treated patients had significantly less cervical shortening than the placebo group. A significant difference was also observed between groups for categorical outcomes including the frequency of cervical length progression to ≤25 mm and a ≥50% reduction in cervical length from baseline in this subpopulation [67]. Further research is necessary and several randomized trials are underway to clarify the efficacy and fetal safety of progesterone treat.

Cervical cerclage is an old, easily performed procedure for treatment of true cervical incompetence [77]. Dijkstra et al. studied 80 women whose primary physician determined that a prophylactic ($n = 50$) or urgent cerclage ($n = 30$) was indicated and had transvaginal ultrasonographic evaluation before and after cerclage. They found that the mean ± standard deviation precerclage cervical length was 27.2 ± 10.3 mm and after cerclage was 34.1 ± 9.9 mm ($n = 80$, $P < 0.001$). The increase in cervical length after cerclage is not predictive of term delivery [78]. Until recently, cerclage was the only intervention studied to prevent PTB in asymptomatic women with short CL. Rust et al. randomized 113 women with CL < 25 mm or ≥25% funneling measured between 16 and 24 weeks to either modified bed rest or cerclage. No significant differences between two groups regarding risk of PTB <34 weeks or perinatal death were noted. It is important that women were included based on an incidental finding of a short cervix without taking into account other risk factors in the maternal history. Therefore, the majority of women were considered low risk before the sonographic findings [79]. To et al. also sampled 47,123 asymptomatic women and identified a cervix of 15 mm or less in 470, of whom 253 (54%) were randomized to either cervical cerclage ($n = 127$) or expectant management ($n = 126$). No significant differences in the rate of PTB <33 weeks or in perinatal or maternal morbidity or mortality were noted. Again, women in this study were incidentally found to have a short cervix. Subgroup analysis of the utility of cerclage in the high-risk population, based on maternal history, was not performed [80].

Cerclage is not indicated in low-risk patients. A case-controlled study by Incerti et al. found that cerclage does not reduce PTB in low-risk women with short CL compared with rest alone. However, this is not the case in women with previous PTD. However, this is not the case in women with previous PTD [81]. A recent multicenter randomized trial included 302 women with at least one prior PTB ≤32 weeks

and TVU CL < 25 mm between 16 and $22^{6/7}$ weeks randomized to either cerclage or no cerclage. PTB <35 weeks was similar in both groups, but the benefit was most pronounced when CL was <15 mm, suggesting the presence of a more significant, and treatable, component of cervical insufficiency [82]. The systematic meta-analysis by Berghella et al. has shown that Cerclage, when performed in women with a singleton gestation, previous preterm birth, and cervical length <25 mm, seems to have a similar effect regardless of the degree of cervical shortening, including CL 16–24 mm, as well as CL ≤ 5.9 mm [83].

Weekly intramuscular 17-alpha-hydroxyprogesterone caproate (17 P) was compared with McDonald cerclage in women with short CL ≤ 25 mm at between 16 and 24 weeks' gestation. The study was terminated, however, when the interim analysis showed no difference in PTD <35 weeks between treatment groups. However, cerclage may be more effective in preventing spontaneous PTD in women with CL ≤ 15 mm [84]. In another study, Berghella et al. showed that 17 P had no additional benefit for prevention of PTD in women who had prior SPTD and got ultrasound-indicated cerclage for CL < 25 mm. In women who did not get cerclage, 17 P reduced previable birth and perinatal mortality [85].

Evaluation of the cervical morphology and biometry with transvaginal ultrasonography at 16–24 weeks of gestation is a useful tool to predict the risk of preterm birth in low- and high-risk singleton pregnancies. For instance, a sonographic cervical length >30 mm and present CGA have a 96-97% negative predictive value for preterm delivery at <37 weeks. Transvaginal evaluation of cervix during routine fetal morphological examination helps identify asymptomatic low- and high-risk women for prediction of preterm delivery. Available evidence supports the use of progesterone to women with cervical length ≤25 mm, irrespective of other risk factors. In women with prior spontaneous PTD with asymptomatic cervical shortening (CL ≤ 25 mm) there should be prophylactic cerclage procedure and weekly to every two weeks follow-up.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2011, Article ID 941057, 5 pages
doi:10.1155/2011/941057

Review Article

Prevention of Preterm Labour: 2011 Update on Tocolysis

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Received 3 May 2011; Accepted 27 September 2011

Academic Editor: Yves Jacquemyn

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The aim of this paper is to review available data about drugs for preventing preterm labour. Tocolytic therapy includes β adrenergic receptor agonists, NO donors, magnesium sulphate, prostaglandin-synthase inhibitors, oxytocin receptor antagonists, calcium-channel blockers, progesterone, 17-α-hydroxyprogesterone caproate, and antibiotics. Their specific effects on myometrial contractility, their safety, their efficiency, and side effects profile for the mother and the fetus are presented. The main question of why and for what reasons tocolysis should be administrated is discussed.

1. Introduction

Preterm delivery is defined by a birth occurring before 37 weeks of gestation or before 259 days from the last menstrual period. Prematurity is multifactorial and its incidence has increased during the last decade in most occidental countries, probably due to increased risk factors responsible for elective prematurity [1–3].

The mechanisms for preterm labour are still unclear. It could be associated either with a premature activation of the physiological contracting process or with a pathological factor responsible for uterine contractions, leading to preterm delivery [1–3].

Among identified pathways for preterm labour, there are uterine overdistension due to multiple pregnancies or polyhydramnios, placental ischaemia, cervical disease, immunologic and allergic phenomena, decidual or retroplacental haemorrhage, fetal endocrine activation intrauterine infections, and inflammatory processes. Elective prematurity due to maternal or foetal conditions is becoming a significant cause [1–4].

Tocolytic drugs have been available for several decades but their actions are directed toward the effects and not the causes of preterm labour [1, 3, 5].

Therapeutic strategies available in the literature for stopping preterm labour are discussed in this paper. Their efficacy depend on an early and accurate diagnosis of the condition, the fetal fibronectin, and cervical length ultrasonography [2].

Drugs safety and side effect profile is a major concern not only for the pregnant women but also for the foetus [4–6]. In some clinical conditions such as abruptio and chorioamnionitis, inhibition of uterine contractions and birth delay may be more harmful in terms of outcome and should be avoided [2, 3]. Another concern is the administration route and the optimal range of gestational age for these treatments [5].

Tocolysis aims not only to inhibit uterine contractions but also to allow a safe transfer of the pregnant patient to a tertiary care centre. It gives the opportunity to administrate corticosteroids for preventing neonatal risks associated with prematurity [5–7].

2. Mechanisms of Tocolysis

Myometrial contractility is a complex process based on myocytes function. It involves the presence of hormonal receptors, ions channels, intercell gap junctions, and regulatory proteins such as oxytocin, endothelin, tachykinin, and angiotensin [8, 9]. The increase of intracellular calcium concentration is essential for the uterine smooth muscle contraction [9].

As shown on Figure 1, uterine relaxation may be obtained by interfering with an intracellular messenger responsible for contractile proteins effects: β adrenergic receptor agonists, nitric oxide (NO) donors, magnesium

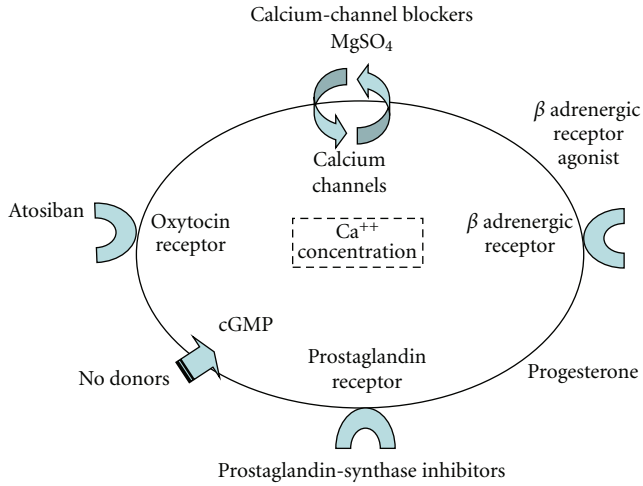

Figure 1: Mechanisms of action for tocolytics.

sulphate and calcium channel blockers are tocolytic drugs aiming to this [1, 2, 6, 9]. Another pathway involves the inhibition of contracting factors synthesis or effect. Atosiban, an oxytocin receptor antagonist and prostaglandin-synthetase inhibitors have this effect by interfering with endogenous myometrial stimulators [1, 2, 6, 9].

3. Types of Tocolytic Treatment

3.1. β Adrenergic Receptor Agonists. Selective β 2 agonists such as ritodrine and salbutamol have been used in clinical practice for preterm labour since the 1980s. These drugs impair intracellular cyclic AMP concentration and facilitate myometrial relaxation [9, 10]. Randomized controlled studies and meta-analysis reported that these agents were more efficient than placebo for delaying preterm birth for two days. Unfortunately, no benefit for long-term (tocolytic effect restricted to 7 days) and perinatal mortality and morbidity rate was found [5, 10, 11]. Moreover, even with selective β 2 adrenergic receptor agonists, there are significant maternal side effects reported such as tachycardia, dyspnoea, hypokalemia, hyperglycemia, and chest pain [5, 6, 9–12]. In conclusion, despite their efficiency, β 2 agonists' safety profile is a real concern responsible for therapy discontinuation and choosing alternative tocolytic drugs.

3.2. NO Donors. NO is a powerful vasodilator synthesized during an amino acid oxidation process catalysed by NO synthase. It is present in myometrial cells and increases cGMP content by interaction with guanylyl cyclase. There is a specific link between NO production and uterine relaxation [8, 9].

Transdermal nitroglycerin administration has been used in preterm labour but only in small series. It was associated to a better tocolytic effect than placebo on delaying delivery for two days. Its effect was similar to ritodrine [2–5]. As there is no large randomized studies available, NO is not used in clinical routine.

3.3. Magnesium Sulphate. The relaxant effect of Magnesium sulphate in vitro and in vivo on human uterine contractility has been widely reported. As magnesium is a calcium antagonist, it decreases calcium intracellular concentration and inhibits contraction process [2, 4, 9]. However, in 2002, a meta-analysis based on 881 patients did not evidence any benefit of Magnesium sulphate administration over placebo use in preterm labour [13]. As the drug is crossing the placenta, there were concerns about fetal safety. An increased risk of perinatal death and neonatal adverse effects including neurological and metabolic disorders were reported in some trials using Magnesium sulphate treatment at high dosage [6, 13]. It can also affect maternal neuromuscular system. Over a serum concentration of 9 mg/dL, there is a high toxicity risk resulting in respiratory depression and disappearance of reflexes. There is no evidence any more to recommend this drug as a first-line tocolytic agent [2, 6, 13, 14].

However, when administered prophylactically at low dose, it was reported to have a neonatal neuroprotective effect in a randomized multicentre trial [15] but this effect should be confirmed in the next future on large randomised controlled studies [16].

3.4. Prostaglandin-Synthase Inhibitors. Prostaglandin-synthase or cyclooxygenase (COX) isoforms COX-1 and -2 are essential enzymes for converting arachidonic acid to prostaglandins. Prostaglandins are well-known uterine contraction inducer by enhancing myometrial gap junction and increasing intracellular calcium concentration [2, 4, 5, 9]. Indomethacin, a nonspecific COX inhibitor, has been reported in studies and in a recent meta-analysis to be an efficient tocolytic drug compared to placebo, significantly delaying preterm delivery [11]. It can be administrated rectally or orally. Its use should be restricted in duration and limited to pregnancies below 32 weeks because of fetal ductus arteriosus closure risk and decreased urine production responsible for oligohydramnios [3, 5, 6, 17]. These treatments also have maternal side effects including gastric ulcer or asthma recurrence [3, 5, 6]. COX-2 inhibitors such as nimesulide or rofecoxib have been studied in animal but not yet in humans and are not actually recommended for preventing preterm labour in clinical practice [18]. In conclusion, indomethacin is an efficient tocolytic drug with no serious adverse drug reaction and is indicated for short-term effect during the second trimester of pregnancy.

3.5. Oxytocin Receptor Antagonists. These agents are in competition with the myometrial and decidual oxytocin receptors. The only drug used in clinical practice is atosiban. It blocks in a reversive manner the intracytoplasmic calcium release associated with contractions and downregulates prostaglandin synthesis [2, 9]. A first multicentric randomised trial comparing atosiban and ritodrine demonstrated a similar tocolytic effect but fewer adverse effects with atosiban [4, 6]. A meta-analysis published in 2005 reported no benefit in terms of preterm delivery rate and neonatal outcome in 1695 patients treated either by atosiban or placebo [19]. This study was responsible for the FDA nonapproval of atosiban in the USA. However, in Europe, many studies were carried out and did not confirm it.

Atosiban is widely used in clinical practice because of its low side effects profile [5, 6]. A german meta-analysis based on 6 randomised trials, among them 3 double blind studies, confirmed a similar tocolytic action for atosiban and β adrenergic receptor agonists. A significantly low incidence of adverse effects is reported. Moreover, a lower cost saving in terms of hospital length and extra tests for excluding morbidity causes is found for the atosiban treated patients when compared to continuous fenoterol administration controls [12]. In conclusion, atosiban seems to be an adequate therapeutic choice for effective tocolysis with a low maternal and fetal adverse effects profile.

3.6. Calcium-Channel Blockers. These agents are interfering with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration and induce myometrial relaxation [2–4].

Nifedipine is the most commonly used drug for preterm labour inhibition at a daily dose of 30–60 mg daily. Randomised controlled trials report a similar tocolytic effect for nifedipine compared with β adrenergic receptor agonists [20]. Unfortunately, there is no placebo-controlled studies available to confirm it. A Cochrane Database review meta-analysis published in 2003, reported a decreased number of deliveries within 7 days following treatment and also, a reduced incidence of neonatal respiratory distress syndrome [21]. A recent systematic review based on 26 trials and 2179 patients confirms a higher efficiency and a lower side effects incidence in the nifedipine group compared to β adrenergic receptor agonists-treated patients [22]. These data confirm that nifedipine is a efficient tocolytic agent, with an easy oral route of administration, few side effects, and a low neonatal complications rate. However, it should be used with caution in patients with compromised cardiovascular condition as they may be at risk of pulmonary oedema and cardiac failure [5].

3.7. Progesterone and 17-α-Hydroxyprogesterone Caproate. Progesterone is a steroid hormone secreted by the corpus luteum and by the placenta after 8 weeks of gestation. It has a physiological effect on uterine quiescence mediated by a direct effect on intracellular calcium concentration and prostaglandin synthesis [1, 2, 5, 9]. Several randomised trials reported a significantly reduced incidence of preterm birth in patients at risk treated either with weekly intramuscular 17-α-hydroxy progesterone caproate [23] or daily vaginal micronized progesterone [24, 25] from 24 to 34 weeks. But these treatments showed no benefit in terms of perinatal mortality and morbidity [2, 5, 23–25]. The vaginal route of progesterone administration is associated with less side effects such as sleepiness and headaches [4, 5]. Although these treatments seem effective in patients with previous history of preterm birth or with a short cervix, it is essential to collect more data in large randomised controlled trials for confirming its potential benefit in the prevention of preterm delivery.

3.8. Antibiotics. Infection is one of causal factors of preterm labour with an incidence of 20–40%, especially before 30 weeks [1, 2]. Antibiotics use for preventing preterm labour has been largely studied [5, 28–30]. In the presence of preterm labour with intact membranes, the prophylactic administration of antibiotics is not recommended as there is little evidence of benefits [28]. But if there is a preterm rupture of the membranes (PROM), a meta-analysis based on 22 studies including more than 6000 patients, shows a significant decrease of preterm delivery and chorioamnionitis rate in the treated group [29]. Neonatal complications were also lower in this population [4, 29]. In bacterial vaginosis associated with pregnancy, antibiotics were found to eradicate infection but they showed no effect on the incidence of preterm delivery [30]. In conclusion, PROM is the only clinically proved indication for using antibiotics in order to prevent preterm birth [29].

4. Discussion

There are many possible interventions aiming to treat this multifactorial syndrome called preterm delivery. As described here, only some drugs have been proved to be effective on the contraction process, but there are no clear evidence of associated improved neonatal outcome. Some drugs are used as first-line single therapy such as β adrenergic receptor agonists and atosiban in Europe [11, 12]. In severe cases, combined therapy could be offered but should be restricted because of adverse effects addition. A Dutch prospective study based on 1920 women, reported that the overall incidence of severe adverse effect is doubled when a multiple-drug regimen is chosen [27]. The literature review evidences that there are still insufficient data regarding some therapies such as the effectiveness of progesterone in the absence of previous medical history and the role of antibiotics, bed rest, and maintenance therapy [5, 31].

Specific conditions are subject to discussion: in multiple pregnancies, expanded blood volume and anaemia may predispose to pulmonary oedema when tocolytic agents such as β adrenergic receptor agonists, magnesium sulphate, and calcium channel blockers are prescribed. In these pregnancies, atosiban, with its low side effects incidence, seems to be the safest choice.

The role of tocolysis in PROM allows pregnancy prolongation for corticosteroids administration but has not been reported to significantly improve neonatal outcome [32]. Is long-term therapy effective? There is no clinical evidence on published trials and systematic review to justify tocolytic therapy maintenance except for atosiban [31].

A critical review about tocolysis points to the potential risk of delaying preterm delivery specially in case of infectious or inflammatory process and does not evidence an improved neonatal outcome as tocolysis is often associated with corticosteroids administration [26].

5. Conclusions

Prevalence of preterm birth has increased during the last decades and it is a real public health concern. Management with tocolytic drugs aims to stop uterine contractions and to prevent neonatal risks associated with prematurity by in

Table 1: Effects of currently used tocolytic drugs.

Drugs	Effects	Outcome	Side effects	Studies
β AdRA	Decrease cAMP	Delay D 2–7 days	Cardiovascular	RCT [5, 11, 12]
			Metabolic	Meta-analysis [2, 10]
NO donor	Increase cGMP	Delay D 2 days	Cardiovascular	Small series [2, 5]
$MgSO_4$	Decrease IC Ca++	No tocolytic effect	Neurological	RCT, meta-analysis
			Metabolic	[2, 4–6, 13, 14]
			Perinatal mortality	
		Fetal neuroprotection		RCT [15, 16]
PgSI	On gap junction	Delay D 2–7 days	Gastrointestinal	RCT, meta-analysis
	Decrease IC Ca++		Fetal kidney function	[2, 4–6, 17, 18, 26]
			Premature closure ductus arteriosus	
Ox RA	Competition with receptor binding	Controversial efficiency	IUGR? Mortality?	Review [2]
			Few side effects	RCT, meta-analysis
				[4, 5, 9, 11, 12, 19, 27]
Ca++ CB	Decrease IC Ca++	Delay D 7 days	Cardiovascular	No placebo RCT
		Decreased neonatal morbidity		Comparative RCT
				[2, 4, 9, 20–22]
Progesterone	Reduction preterm delivery in high-risk patients			RCT [23, 25]
	Decrease IC Ca++		Sedative	
	Decrease Pg synthesis		Liver cytolysis	[24, 26]

utero transfer of the pregnant patient in a tertiary specialized centre and by corticosteroids administration [1, 2, 7].

Our review of several studies and meta-analyses reported on Table 1 confirm the efficacy of β adrenergic receptor agonists, prostaglandin-synthetase inhibitors, and atosiban for delaying delivery for 24–48 hours [2, 5, 6, 10, 11, 17].

In terms of maternal and fetal safety, the overall prevalence of severe side effects associated with tocolysis is around 1% and is more frequent in multiple therapies, multiple gestation, and preterm rupture of the membranes [27]. Atosiban is our first choice drug for safety, followed by prostaglandin-synthase inhibitors and nifedipine [2, 5, 6, 12, 27].

For the future, tocolytic drugs development should aim to reach a better efficacy in terms of pregnancy prolongation and a lower adverse effects profile. A better understanding of the regulation of myometrial contractility and the detection of specific maternal or fetal parameters should be used for new tocolytic strategies. Last generation of oxytocin receptor antagonists such as barusiban could be more efficient and have less affinity for the vasopressin receptors [9]. Specific COX-2 inhibitors or "coxibs," prostaglandin receptors antagonists could be promising tocolytic alternatives [2, 4, 9, 18].

Abbreviations

β AdRA: β adrenergic receptor agonist
$MgSO_4$: Magnesium sulphate
PgSI: Prostaglandin synthase inhibitor
Ox RA: Oxytocin receptor agonist
Ca++ CB: Calcium channel blocker
Delay D: Delay for delivery
RCT: Randomized controlled trial
DA: Ductus arteriosus
IC Ca++: Intracellular calcium concentration
IUGR: Intrauterine growth retardation.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2011, Article ID 164654, 8 pages
doi:10.1155/2011/164654

Review Article

Relationship between Periodontal Diseases and Preterm Birth: Recent Epidemiological and Biological Data

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Received 1 April 2011; Accepted 3 October 2011

Academic Editor: Yves Jacquemyn

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For ten years, the incidence of preterm birth does not decrease in developed countries despite the promotion of public health programs. Many risk factors have been identified including ethnicity, age, tobacco, and infection. However, almost 50% of preterm birth causes remain unknown. The periodontal diseases are highly prevalent inflammatory and infectious diseases of tooth supporting tissues leading to an oral disability. They influence negatively general health worsening cardiovascular diseases and diabetes. Periodontal diseases have been also suspected to increase the rate of preterm birth, but data remain contradictory. The objective of this review is to present the principal results of epidemiological, biological, and interventional studies on the link between periodontal diseases and preterm birth. The conclusions of this work underline the importance for the physician/obstetrician to identify women at risk for preterm birth and to address these patients to dentist for periodontal examination and treatment in order to limit adverse pregnancy outcomes.

1. Introduction

Preterm birth is defined as any delivery that occurs after 23 gestational weeks and less than 37 weeks [1, 2]. This is a major determinant of neonatal morbidity and mortality [3]. Furthermore, preterm birth has long-term consequences for infant including an increased risk of neurological impairments and behavior disorders and higher rates of chronic health disorders than children born at term [4]. Global incidence of preterm birth is around 9.6% of all birth representing 12.9 million births [5] with regional disparities: 12% to 13% in the USA, from 5% to 9% in Europe [6], and 18% in Africa [7]. For ten years, the rate of preterm birth does not decrease in most of the industrialized countries. In the USA preterm birth prevalence increased from 9.5% in 1981 to 12.7% in 2005. Furthermore, women classified as black, Afro-American and Afro-Caribbean, are frequently reported to be at higher risk of preterm birth [7]. Preterm birth rates are in the range of 16–18% in black women compared with 5–9% for white women in USA [2]. Many preventive treatments have been proposed to decrease risk of preterm birth especially for women at risk. Many countries have programs offering special assistance to these women including advice and counseling (about nutrition, drugs, tobacco), assistance (transportation to clinic appointments, household help), and emotional support [8]. Obstetric treatments are possible including treatment with tocolytic agents, antenatal corticosteroids and antibiotics, and optimum timing of indicated preterm birth. These measures are intended to reduce the burden of prematurity-related illness more than to reduce the rate of preterm birth and have effects on perinatal morbidity [9].

The role of many risk factors have been shown by results of epidemiological studies such as increasing age of women giving birth, ethnical origin, tobacco, socioeconomic disparities, maternal body-mass index, or multiple pregnancies [5, 10–12]. Mother's health is also an important factor influencing pregnancy outcome. Cervical incompetence or short cervical length, preeclampsia and numerous maternal infection, systemic like toxoplasmosis [13, 14] and local infections such as bacterial vaginosis, chorioamnionitis, or uterine track infections [2, 15–17] increase the risk of preterm birth. Unfortunately, around 50% of causes of preterm birth remain unknown [16]. In 1996, Offenbacher et al. introduced the hypothesis that periodontal diseases could be a potential risk factor for preterm birth [18]. Since,

many epidemiological or interventional studies have been performed to explore this relationship.

2. Periodontal Health and Pregnancy: A Reciprocal Relationship

The periodontal diseases are inflammatory diseases of gum and tooth supporting tissues caused by the oral bacterial biofilm containing almost 300 different species [19–21]. Different forms of periodontal diseases are observed. The superficial, reversible, and relatively harmless form corresponds to the gingivitis, and the profound and irreversible form corresponds to the periodontitis [20].

Gingivitis is a common pathology that affects everyone in his life (prevalence 80 to 100%). It corresponds to an inflammation of superficial soft tissues around teeth initiated by supragingival biofilms accumulation. The principal clinical signs are bleeding during tooth brushing or mastication, gum swelling, and gingival pains. Gingivitis is due to an absence or inappropriate oral hygiene habits and is worsened by local factor increasing dental plaque retention including supragingival calculus, retentive crown or dental misalignment, and absence or irregular dental cares. Consequently, oral hygiene education, scaling, and monitoring are very efficient to treat and prevent gingivitis [22].

The prevalence of periodontitis is about 60% with a pick of incidence at 60 years [20]. Periodontitis correspond to an inflammation of superficial and profound periodontal tissues caused by supra- and sub-gingival biofilms and leading to an irreversible destruction of tooth supporting tissues. The pathognomonic clinical sign of periodontitis is the formation of periodontal pockets. The others classical associated signs are gingival bleeding, gingival retraction, long appearance of teeth, tooth mobility, halitosis, abscess, bone loss, tooth mobility, and in the most severe cases, spontaneous tooth loss [20]. Two principal forms of periodontitis are recognized. The chronic form progresses slowly on many decades and displays successive phases of activity. Older patients may present severe form of chronic periodontitis with a consequent bone loss. However, in patients suffering from chronic periodontitis, the number of teeth lost for periodontal reasons is generally low. The aggressive form affects less than 10% of the general population. This form is predominant in young population and could lead to an important loss of teeth in few years [23]. This form is characterized by a strong inflammatory response and a rapid, profound, and generalized destruction of periodontal tissues associated to the presence of virulent bacteria such as *Porphyromonas gingivalis (Pg)*, *Aggregatibacter actinomycetemcomitans (Aa)*, and *Treponema denticola* [21] (Figure 1). Finally, the evolutions of chronic and aggressive periodontitis and at a lesser extent the evolution of gingivitis are markedly and negatively influenced by many risk factors such as tobacco, diabetes, low socioeconomic status, and ethnic origin. For instance, Africans have a higher prevalence of aggressive forms of periodontitis [24–26].

The diagnosis of gingivitis and periodontitis is generally based on clinical symptoms described above; however, be recognized by patient himself. Many studies based on self-report have shown that patients were able to evaluate correctly but grossly their periodontal status [27]. However, the evaluation of periodontitis severity requires a specific examination based at least on a periodontal probing performed by a periodontist or a general dentist. The periodontal pocket depth associated to gingival bleeding measurement could be considered as the best markers of periodontal disease activity or the inflammatory/infectious burden of periodontitis. The measurement of clinical attachment level (periodontal pocket depth plus gingival recession) and bone loss around teeth reflect more the history and the severity of periodontal disease.

The aim of periodontitis treatment is to reduce periodontal tissues infection through a rigorous oral hygiene education and a mechanic treatment (scaling, root planning, and surgery) [20], associated to a chemical antimicrobial therapy including the administration of systemic antibiotics in the severe chronic or aggressive forms of periodontitis [28]. Patients must also attend regular visits to dentist or periodontologist to control and maintain periodontal treatment results. These treatments decrease efficiently periodontal tissue inflammation and eliminate the more virulent periodontal pathogens. They stop the destruction of periodontal tissues and prevent tooth loss [29–31]. Furthermore, they improve some systemic conditions (glycemia, lipid metabolism, endothelial function) [32–35]. However, the initial severity of periodontitis and the persistence of risk factors such as smoking and diabetes considerably impair periodontal treatment results [31, 36].

Interestingly, pregnancy influenced also periodontal status. Pregnant women are more susceptible to inflammation and display an increase of gingival bleeding on probing. Pregnant women present generally periodontal pocket due to gingival swelling rather than periodontal tissue breakdown [37]. These periodontal pockets disappear after delivery. However, in women suffering from periodontitis before their pregnancy, it appears that pregnancy could lead to an increase of periodontal disease severity [38]. Hormonal modifications have been proposed to exacerbate gingival inflammation, to initiate changes in the composition of oral biofilm, and to induce a selective growth of periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia* [39], or *Campylobacter rectus* [40].

3. Epidemiological Link

During the last decade, numerous epidemiological studies have been conducted on the association between preterm birth and periodontitis [3]. More or less strong associations between periodontal status and preterm birth alone (PB), low birth weight (LBW), or preterm birth associated to low birth weight (PLBW) have been shown in cohort/cross-sectional studies by Lunardelli and Peres [41] (Brazil, PB $P < 0.02$), Offenbacher et al. [42] (USA, PB $P = 0.013$), López et al. [43] (Chile, PLBW $P < 0.0004$ and RR = 3.5), Siqueira et al. [44] (Brazil, PB $P < 0.001$), Rajapakse et al. [45] (Sri Lanka, PB OR = 2.3), Toygar et al. [46] (Turkey, PB and PLBW $P < 0.01$), Agueda et al. [47] (Spain, PB

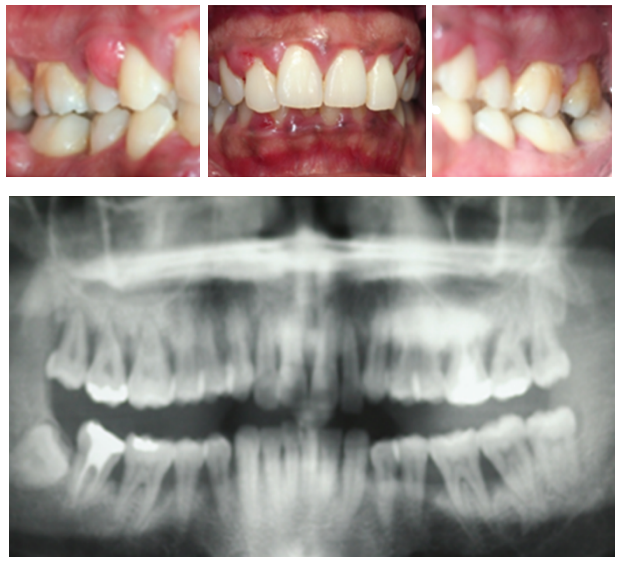

Figure 1: Clinical views of aggressive periodontitis affecting pregnant women. Major clinical signs are gingival inflammation and alveolar bone destruction. *(Courtesy to Dr. Bouaziz W).*

OR = 1.77), and Heimonen et al. [48] (Finland, PB $P < 0.001$), and also in case-control studies by Gomes-Filho et al. [49] (Brazil, PLBW OR = 2.1), and Khader et al. [50] (Jordan, PLBW $P < 0.0001$). However, some other investigations did not find a significant association, such as cohort studies by Moore et al. [51] (PB, LBW), Noack et al. [52] (Germany, PLBW), Agueda et al. [47] (PLBW), Nabet et al. [53] (France, PB), and case-control studies by Davenport et al. [54] (UK, PLBW), Bassani et al. [55] (Brazil, PLBW), and Vettore et al. [56] (Brazil, PB, and PLBW). The different conclusions of these studies could be explained by the use of different definitions of adverse pregnancy outcomes, for instance PB versus PLBW and periodontal disease definitions, reflecting in fact different pathologic entities and disease severities [57, 58]. Indeed, the periodontal status assessment of pregnant women is mainly based on threshold numbers of sites with prespecified values of periodontal pocket depth and/or clinical attachment loss [41, 43, 47, 49, 59, 60] but could also be determined by the use of other composite index such as Community Periodontal Index for Treatment Need (CPITN) [48, 54] or other clinical signs including bleeding on probing [45]. Interestingly, the use of variable periodontitis definitions could reverse the association in some cases, especially in cohort studies [56, 58]. However, a high prevalence of severe periodontitis is frequently associated with PB and/or LBW [44, 47, 49, 60, 61] while a low prevalence (7.2%) is not [51]. Furthermore, the strength of the association between periodontal disease and preterm birth incidence increases frequently with the severity of periodontitis [7, 42, 49, 55, 58]. All these data suggest that women populations with a high prevalence of severe periodontitis are at risk for preterm birth.

The risk factors of preterm birth appear to be similar to risk factors for periodontal diseases (tobacco, ethnicity, socioeconomic and educational levels) and may confound the association between periodontitis and preterm birth [3, 7, 62, 63]. Actually, smoking is recognized as one of the principal risk factors for both adverse pregnancy outcomes and periodontitis [17, 64]. In many studies evaluating periodontal status effect on pregnancy, the rate of smoking among pregnant women oscillates between 10 and 20% [41, 42, 46, 49, 55, 56] and is frequently related to periodontitis severity and/or preterm birth but not systematically. The definition criterion of smoking habits and severity, such as the number of cigarettes per day and period of smoking (during and/or prior to pregnancy), vary greatly between studies and may also explain these different results [46, 61]. In some studies ethnicity is correlated with pregnancy outcome and/or periodontal status [42, 51, 63] while other investigations do not report such a correlation [54–56, 65]. In the same way, elevated percentages of pregnant women with no education or only primary education are frequently associated with PB and/or LBW [44, 46, 50] and periodontitis [45], but not systematically [54, 55]. This diversity of epidemiologic study results shows the interest to best define the specificity of periodontal pathology of pregnant women considering their young age and the hormonal influence of pregnancy on periodontal tissues.

4. Biological Hypothesis

Considering epidemiological evidence, biological theories have been proposed to link preterm birth and periodontal diseases [66]. Mainly, three hypotheses are developed

(i) bacterial spreading,

(ii) inflammatory products dissemination,

(iii) role of feto-maternal immune response against oral pathogens.

4.1. Bacterial Spreading. The current paradigm indicates that majority of intrauterine infection originates in the lower genital tract [67]. Despite this statement, number of studies report intrauterine infections caused by species not found in urogenital tract [67]. The bacterial spreading theory is based on the possible dissemination of oral bacteria including periodontal pathogens through blood circulation [68] to the amniotic fluid and leading to chorioamniotic infections. The frequent gingival inflammation of women presenting periodontal diseases [69], especially pregnancy-associated gingivitis [70], facilitates bacteremia process [67]. Furthermore, the more periodontal pockets are deep, the more important is the exchange surface between bacteria biofilm and blood circulation (15 to 20 cm^2 in the most severe cases) [71]. Many analyses of amniotic fluid or placenta have been performed and evidence the presence of different oral pathogens such as *Bergeyella*, *Eikenella* [67], *Fusobacterium nucleatum,* or *Porphyromonas gingivalis* [72–74]. Inside uterus, these pathogens could provoke an inflammatory response. The increase of inflammatory cytokines or metalloproteases synthesis and the neutrophil activation could induce preterm birth process [67].

In vivo studies show that the invasiveness of uterine tissues largely depends on the type of bacteria. In a sheep model of intra-amniotic injection of lipopolysaccharide from different bacterial species, it appears that periodontopathic lipopolysaccharides induce a high rate of fetal lethality [75]. Furthermore, in a rat model, placenta colonization by *Porphyromonas gingivalis* is dose and strain dependent [76]. Potential pathological mechanisms of certain periopathogens, especially for *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been studied. For example, *Porphyromonas gingivalis* could infect syncytiotrophoblasts, chorionic trophoblasts, decidual cells, and amniotic epithelial cells [74] and promotes inflammatory process trough Toll-like receptor 4 [77].

Finally, a case-report study has been published in 2010 concerning a stillbirth caused by *Fusobacterium nucleatum* from the mother's mouth [78]. This study highlights the fact that an oral periodontal pathogen can, by hematologic pathway, colonize placenta and provoke fetal complications. It is important to notice that such colonization may be dependant from mother's immunological status.

4.2. Hematogenous Dissemination of Inflammatory Products. Acute inflammation is responsible for a substantial fraction of preterm birth [79]. In 1998, Offenbacher et al. suggested that the cytokines produced by local inflammation in periodontal tissues affected by periodontitis have systemic effects after diffusion of such cytokines through blood flow [80]. Locally, studies show that periodontal diseases increase secretion of several cytokines, notably PGE-2, TNF-α, IL-6 or IL-1β [81, 82]. Analysis of amniotic fluid obtained at the time of preterm birth shows elevated levels of inflammatory cytokines [83]. We hypothesize that cytokines produced in periodontal tissues promote inflammation in maternal-fetal unit. Clinically, high gingival crevicular fluid levels of PGE-2, IL-1β, or Il-6 have been associated with their elevated levels in amniotic fluid [80, 84]. The inflammatory response appears to be the privileged pathway of the pathogenic periodontal disease influence on pregnancy, as suggested for other major systemic diseases including cardiovascular diseases or diabetes [85].

4.3. Fetomaternal Immune Response. The immune and genetic characteristics of fetus and pregnant women are one of the potential mechanisms linking periodontal diseases to preterm birth. Numerous studies have analyzed fetal and maternal antibodies directed against oral pathogens during pregnancy. In the study of Boggess et al., 35.2% of samples are Ig-M positive for at least one oral pathogen, and 26.6% are positive for more than one. The presence of Ig-M is associated to an increased risk of preterm birth [86]. This immune response against oral pathogens could be associated with an inflammatory response, and the synergy between the two mechanisms increases significantly the risk [86]. The genetic predisposition is also important. Polymorphisms of genes coding for proinflammatory cytokines such as TNF-α, IL-1 or IL-6 are associated to a hyperinflammatory response. The consecutive overexpression of these cytokines increases the risk of preterm birth [87–89].

The mechanisms linking periodontal diseases and preterm birth are not well defined. Further investigations should be performed to evaluate the impact of each theory. Nevertheless, we hypothesized that the influence of periodontal diseases on preterm birth is the result of an inflammation of the fetomaternal unit that is amplified in women presenting particular phenotype.

5. Effects of Periodontal Treatment on Preterm Birth Incidence

Considering periodontal diseases as a risk factor for preterm birth, interventional studies have been performed to evaluate impact of periodontal treatment on pregnancy outcomes. Case-control studies including a relative large number of pregnant women (>400) show some apparent contradictory results and different conclusions [43, 90–94]. Indeed, the periodontal treatment may improve periodontal conditions and/or pregnancy outcomes [43, 90, 94] or not [91, 93]. A recent meta-analysis indicates that the treatment of periodontal diseases does not reduce the rate of preterm birth [95]. However, as discussed above for epidemiological studies, the conclusions of this analysis could be balanced by the relative heterogeneity of studied populations, according to risk factors ethnicity, smoking, socioeducative levels, and periodontal status definition. For instance, the percentage of black people varies considerably between studies: 50% to 65% of Hispanic and Caucasian [38, 43]); 45% to 87% of Afro-American [90, 93]. Furthermore, the modalities of periodontal care in the different studies display some differences that may influence periodontal outcomes. A first session of etiologic periodontal treatment, including oral hygiene instructions, scaling, and root planning was generally performed at the end of the first trimester of

pregnancy (before 20 to 28 weeks). This first session could be unique [91, 93] or reinforced by regular control visits and complementary treatments if necessary until delivery [43, 90]. The local effects of periodontal treatments are generally positive [43, 90]. Gingival inflammation and mean probing pocket depth are reduced, especially in study using reinforced periodontal treatment modalities [43, 90]. However, a relative high rate of patients demonstrating a periodontitis progression is observed in some studies (70% [91], 50% [90], 68% [94]) suggesting that periodontal treatments do not work so efficiently than in a general population [91]. Indeed, the relative "narrow therapeutic window" to perform periodontal treatment and to obtain a successful periodontal lesion cicatrisation, and the aggressive profile of severe periodontitis in young women could be considered as limiting factors [91, 94]. A recent study performed by Jeffcoat et al. [94] confirms that the efficiency of periodontal treatment should be considered before the analysis of results. In this study, 322 pregnant women with periodontal disease have been followed, 160 have received randomly complete periodontal treatment, and 162 have served as control without treatment. No significant difference was found in term of preterm birth incidence between the two groups. However, after considering the effect of periodontal therapy, the results demonstrate a strong and significant relationship between successful periodontal treatment and full-term birth ratio (odds ratio = 6.02) [94].

Despite apparent conflicting data, the majority of studies report that periodontal treatment is safe for pregnant women and improve periodontal status [3, 90, 92, 94]. The pregnant woman is a particular patient. In order to decrease the impact of periodontal disease on preterm birth incidence, the early diagnosis promotion of periodontal disease for young women especially for those presenting major risk factors should be recommended. The preventive oral care is the best way to prevent oral diseases and their consequences on pregnancy [96]. In case of periodontal disease diagnosis done during pregnancy, a frequent monitoring of the patient should be positive for the control of the disease and the decrease of preterm birth risk. For severe or aggressive periodontitis, metronidazole or amoxicillin could be used in addition to mechanical treatments. Studies have been performed on the effect of antibiotic on rate of preterm birth concerning bacterial vaginosis. The majority of them demonstrates no deleterious effect of antibiotic use on pregnancy outcome especially for metronidazole [97].

6. Conclusion

Periodontal diseases appear to be a potential risk factor for preterm birth. As well as other modifiable risk factors, these diseases must be taken in charge. Cooperation between obstetricians or general practitioners and periodontists should be developed. The promotion of the early detection and treatments of periodontal disease in young women before and during pregnancy will be beneficial especially for women at risk.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2011, Article ID 848794, 7 pages
doi:10.1155/2011/848794

Review Article

Use of Continuous Electronic Fetal Monitoring in a Preterm Fetus: Clinical Dilemmas and Recommendations for Practice

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Received 1 April 2011; Accepted 24 May 2011

Academic Editor: Yves Jacquemyn

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The aim of intrapartum continuous electronic fetal monitoring using a cardiotocograph (CTG) is to identify a fetus exposed to intrapartum hypoxic insults so that timely and appropriate action could be instituted to improve perinatal outcome. Features observed on a CTG trace reflect the functioning of somatic and autonomic nervous systems and the fetal response to hypoxic or mechanical insults during labour. Although, National Guidelines on electronic fetal monitoring exist for term fetuses, there is paucity of recommendations based on scientific evidence for monitoring preterm fetuses during labour. Lack of evidence-based recommendations may pose a clinical dilemma as preterm births account for nearly 8% (1 in 13) live births in England and Wales. 93% of these preterm births occur after 28 weeks, 6% between 22–27 weeks, and 1% before 22 weeks. Physiological control of fetal heart rate and the resultant features observed on the CTG trace differs in the preterm fetus as compared to a fetus at term making interpretation difficult. This review describes the features of normal fetal heart rate patterns at different gestations and the physiological responses of a preterm fetus compared to a fetus at term. We have proposed an algorithm "ACUTE" to aid management.

1. CTG Monitoring of a Preterm Fetus: The Current Status

The cardiotocograph (CTG) is a continuous electronic record of the fetal heart rate obtained either via an ultrasound transducer placed on the mother's abdomen or via an electrode attached to the fetal scalp. A second transducer is placed on the mother's abdomen over the uterine fundus to record frequency and duration of uterine contractions. Both components are then traced simultaneously on a paper strip. Based on current scientific evidence, a CTG is not recommended in the UK as a method of routine fetal assessment of the preterm fetus (<37 weeks gestation) and currently no clinical practice guidelines on intrapartum monitoring of the preterm fetus exist in the UK The International Federation of Gynaecologists and Obstetricians (FIGO) guidelines for interpretation of intrapartum cardiotocogram distinguish 2 levels of abnormalities, suspicious and pathological, however, the gestation to which such criteria can be applied has not been specified. The American College of Obstetricians and Gynaecologists (ACOG) published a practice bulletin on intrapartum fetal heart rate monitoring in 2009. Within this guideline, the decision to monitor the preterm fetus remains vague with recommendations that each case requires discussion between obstetric and neonatal input, in addition to weighing up likelihood of severe morbidity of the preterm fetus (based on gestational age and fetal weight) and issues related to mode of delivery [1]. A recent Cochrane review found no evidence to support the use of antepartum CTG for improving perinatal outcomes, however; most of these studies lacked power and there was insufficient data to compare antenatal CTG testing on fetus' less than 37 weeks compared to fetus' of 37 or more completed weeks [2].

Due to the lack of research and evidence that exists on electronic fetal monitoring (EFM) of the preterm fetus the definition of a normal fetal heart pattern also presents a challenge. Several characteristics of FHR patterns are dependant on gestational age as they reflect the development and maturity of cardiac centres in the central nervous system as well as the cardiovascular system and, hence, differ greatly between

a preterm and a term fetus. Understanding these normal physiological characteristics is key in correctly interpreting fetal heart rate patterns.

2. Factors That Affect Fetal Heart Rate during Labour

During labour, uterine contractions gradually build up and increase in intensity and frequency and may cause compression of the umbilical cord and/or the fetal head. These "mechanical compressions" may result in decelerations in fetal heart resulting in early and variable decelerations, respectively. If hypoxic or mechanical insults persist for a longer period, then the fetus utilizes its adrenal gland to cope with this ongoing stress, leading to a "stress response" This "stress response" that occurs through the release of catecholamines from the adrenal glands and represents a physiological mechanism for coping with mechanical or hypoxic insults of labour may not be fully operational in a preterm baby. This may also be the case when the normal physiological reserves of the fetus may be impaired (intrauterine growth restriction, fetal infection). Inability of a preterm or growth restricted fetus to mount a required stress response may lead to maladaptive responses resulting in permanent hypoxic insult on the fetal brain occurring at a lower threshold than in the term fetus. Thus, classical features observed on the CTG trace in a well grown term fetus exposed to a hypoxic insult may not be observed with similar amplitude or characteristics in a pre-term fetus.

Fetal heart rate is regulated by the autonomic nervous system consisting of 2 branches; the parasympathetic and sympathetic branch which exerts opposing influences on the FHR. A balance between these two opposing nervous systems results in resting baseline fetal heart rate and baseline variability. During fetal development, the sympathetic nervous system that is responsible for survival ("fight or flight" response) develops much earlier than the parasympathetic nervous system ("rest and sleep") that develops during the third trimester. Hence, a preterm fetus may have a higher baseline fetal heart rate with apparent reduction of baseline variability due to unopposed action of sympathetic nervous system.

2.1. Baroreceptors. The parasympathetic nervous system is activated by stimulation of baroreceptors situated in the carotid sinus or aortic arch secondary to increase in fetal systemic blood pressure, leading to a fall in heart rate mediated through the vagus nerve. This is illustrated by a deceleration on a CTG. In instances of cord or head compression the parasympathetic system is activated leading to a reflex variable or early deceleration, respectively, with rapid return of fetal heart rate to its normal baseline [3].

2.2. Chemoreceptors. Chemo-receptors are located peripherally within the aortic and carotid bodies and centrally in the medulla oblongata. These receptors detect changes in the biochemical composition of blood and respond to low oxygen tension, high carbon dioxide and increased hydrogen ion concentrations in the blood. In cases of utero-placental insufficiency, where carbon dioxide and hydrogen ion accumulate with resultant decrease in oxygen concentrations, the chemo-receptors are activated. This results in parasympathetic activation leading to a fall in heart rate, which is protracted and takes longer to recover to baseline rate. These types of decelerations are termed "late" decelerations and due to the accumulation of carbon dioxide and hydrogen ions are more suggestive of metabolic acidosis [3].

2.3. Somatic Nervous System. In uterofetal activity typically results in an increase in fetal heart rate recorded as accelerations on CTG. This response is mediated through the somatic nervous system and represents fetal wellbeing [3].

2.4. Fetal Adrenal Glands. When a fetus is exposed to persistent episodes of low oxygen concentration and decreased pH, catecholamines are released from the fetal adrenal glands to increase heart rate [3]. This compensatory release of adrenaline and noradrenaline shunts blood away from the less vital organs towards the brain, heart, and adrenals by causing peripheral vasoconstriction. This clinical scenario of decelerations, followed by loss of accelerations, subsequent rise in baseline heart rate and gradual loss of variability is typical of a gradually evolving hypoxia (Figure 1).

3. Characteristics of Fetal Heart Rate in a Preterm Fetus

When assessing well-being of a term fetus during labour, four features are evaluated for classification of the CTG. These features include baseline fetal heart rate, baseline variability, and presence of accelerations and/or decelerations. According to National Institute of Health and Clinical Excellence (NICE) guidelines on electronic fetal monitoring in labour, these features, which are present in labour, are further categorized into reassuring and nonreassuring as outlined in Table 1 below.

Characteristics of antepartum and intrapartum fetal heart rate tracings differ in the preterm fetus as compared to a term fetus. Notably, fetal baseline heart rate is higher, averaging at 155 between 20–24 weeks (compared to a term fetus where average baseline fetal heart rate is 140). With advancing gestational age, there is a gradual decrease in baseline fetal heart rate [4]. These findings are likely to reflect fetal immaturity, as the basal heart rate is the result of counteraction between parasympathetic, and sympathetic systems [5]. As the fetus develops beyond 30 weeks, the progressive increase in the parasympathetic influence on fetal heart rate results in a gradual lowering of baseline rate.

Fetal heart rate accelerations are also noted to change with advancing gestational age. Accelerations of fetal heart rate in association with fetal movements occur as a result of fetal somatic activity and are first apparent in the 2nd trimester. Before 30 weeks of gestational age, the frequency and amplitude of accelerations are reduced. Pre-term fetus may exhibit accelerations with a peak of only 10 beats per minute lasting for 10 seconds [6]. With subsequent increase

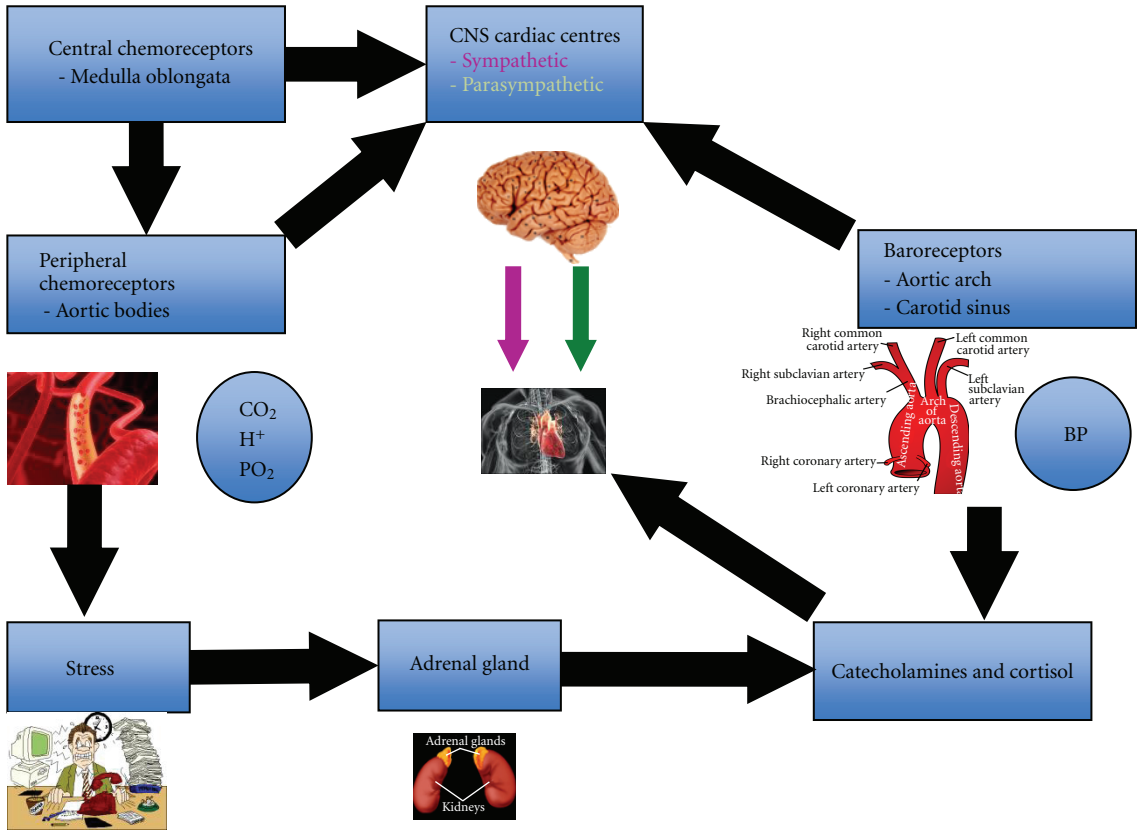

Figure 1: Pathophysiology of fetal heart rate changes.

Table 1: Categorizing individual features of CTG according to NICE guidelines.

Feature	Baseline (bpm)	Variability (bpm)	Decelerations	Accelerations
Reassuring Nonreassuring	110–160 100–109 161–180	>5 <5 for 40–90 minutes	None Typical variable decelerations with >50% of contractions for over 90 minutes. Single-prolonged deceleration for up to 3 minutes.	Present The absence of acceleration with otherwise normal trace is of uncertain significance
Abnormal	<100 >180 Sinusoidal pattern >10 minutes	<5 for 90 minutes	Either atypical variable decelerations with >50% of contractions or late decelerations, both for over 30 minutes. Single-prolonged deceleration for more than 3 minutes.	

in gestational age, the frequency of accelerations increases along with amplitude over the baseline value [6].

Fetal heart rate decelerations in the absence of uterine contractions often occur in the normal preterm fetus between 20 and 30 weeks gestation. As described by Sorokin et al. these decelerations have a lower depth and duration, but can be seen frequently on intrapartum CTG tracings [4]. Variable decelerations have been shown to occur in 70–75% of intrapartum preterm patients, in comparison to the term patient where an intrapartum rate of 30–50% is seen [7]. Several theories have been proposed as a potential explanation for this fetal heart rate pattern, notably decreased amount of amniotic fluid, reduced the Wharton jelly component in the cord of the preterm fetus and lack of development of the fetal myocardium and, therefore, the resultant reduced force of contraction.

Baseline variability may be affected due to incomplete development of autonomic nervous system and subsequent interplay between parasympathetic and sympathetic systems. Variability may also be decreased secondary to the effect of fetal tachycardia present in preterm fetuses. Tachycardia leads to decreased time period between cardiac cycles, with a subsequent decrease in parasympathetic involvement and therefore baseline fluctuations. Reduction in fetal baseline variability in the preterm fetus has been described, however this has not been quantified. Some studies report a higher

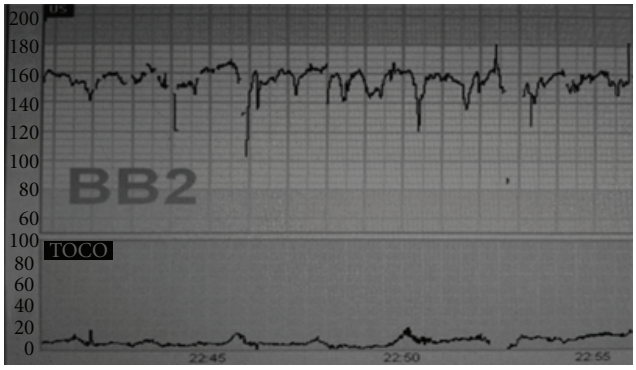

Figure 2: CTG of a fetus at 26 weeks of gestation: note higher baseline heart rate, apparent reduction in baseline variability, and "shallow" variable decelerations.

incidence of adverse outcome following a tracing with reduced variability compared to the presence of decelerations [8].

One of the hallmarks of fetal wellbeing is considered to be "cycling" of the fetal heart rate [3]. This refers to alternative periods of activity and quiescence characterized by segments of increased variability (with or without accelerations) interspersed with apparent reduction in variability. These are believed to reflect Rapid Eye Movement (REM) and non-REM sleep. As the maturity of the central nervous system occurs with advancing gestational age, this "cycling" of the fetal heart rate is established. Hence, in an extreme preterm infant, cycling may be absent and this may be due to functional immaturity of the central nervous system, rather than hypoxic insult.

4. Interpreting Intrapartum CTG at Different Gestations

4.1. 24–26 Weeks. Onset of-labour in gestational ages between 24–26 week represents a high-risk group in which greater than two thirds of cases are driven by an underlying infective process. Other possible factors that may contribute to onset of labour in this group include multiple gestations maternal risk factors such as increased maternal age, raised body mass index (BMI), or pregnancies conceived through in-vitro fertilization (IVF). At this gestation, there is a high risk of neonatal morbidity and mortality, and survival is dependant more on fetal weight and maturity rather than mode of delivery. Hence, continuous monitoring of the fetus during labour, with the view to recognizing features of suspected fetal compromise on CTG and instituting an operative intervention, should be considered with caution. The use of CTG monitoring in this group is contentious and each case should be considered individually with a plan of care agreed following discussion between the patient, obstetrician, and neonatologists. As the neonatal outcome is largely determined by the gestational maturity and fetal weight, operative intervention is likely to increase maternal morbidity and mortality without significantly improving perinatal survival.

Practice Points. Baseline fetal heart rate in this cohort of fetuses is likely to remain at the higher end of normal (between 150–160) due to the unopposed effect of the sympathetic nervous system. Although, the baseline heart rate is expected to be higher, any rate greater than 160 should be still considered to be tachycardic. Persistent tachycardia is likely to arise secondary to iatrogenic causes such as administration of tocolytics (terbutaline) [9]. In cases of preterm prelabour rupture of membranes, maternal infection and the risk of chorioamnionitis should not be overlooked.

Baseline variability and cycling may be reduced at this gestation as a result of impaired development of the parasympathetic component of the autonomic nervous system. Medications such as pethidine, magnesium sulphate and even steroids have also been associated with reduced fetal heart rate variability. However, fetal heart rate variability is an important clinical indicator of fetal acid base balance, especially oxygenation of the autonomic nerve centres within the brain, and absent variability is therefore predictive of cerebral asphyxia. A thorough history of each case should be determined prior to CTG interpretation, and instances where variability is persistently reduced without explanation, should be viewed with caution.

Accelerations at this gestation may not be present or may be significantly reduced with a lower amplitude (rise of 10 beats from the baseline rather than 15 beats). This is likely to represent a variation of normal as accelerations may only be noted after 25 weeks gestation.

Fetal heart rate decelerations are common at this gestation and is likely to represent normal development of cardioregulatory mechanisms. In the presence of other reassuring features of the CTG (as outlined above), these decelerations should not be considered as indicative of hypoxia, and interventions should be avoided based on this parameter alone. Figure 2 shows CTG of a preterm fetus at 26 weeks.

4.2. 26–28 Weeks. Within this group, fetal heart rate tracings will show many similarities to the 24–26 week gestation cohort. After 27 weeks gestation, the frequency of variable decelerations observed is generally reduced [5]. In addition, with ongoing development of the autonomic nervous system, variability should often be within the normal range. Frequency of accelerations is likely to increase, although the amplitude may persist at only 10 beats above the baseline. Likely, iatrogenic causes of fetal heart rate abnormalities (as mentioned above) should also be noted and documented.

Practice Points. Survival in this group is significantly higher than those between 24–26 weeks as survival improves approximately 10% every week during this period. Approximately half of those babies who survive may develop long-term neurological or developmental defects. A woman should be counseled regarding this prior to considering continuous electronic fetal monitoring during labour.

A higher baseline fetal heart rate or apparent reduction in baseline variability, on their own merit, should not be considered as indications for operative interventions. Additional tests of fetal well-being such as fetal blood sampling (FBS)

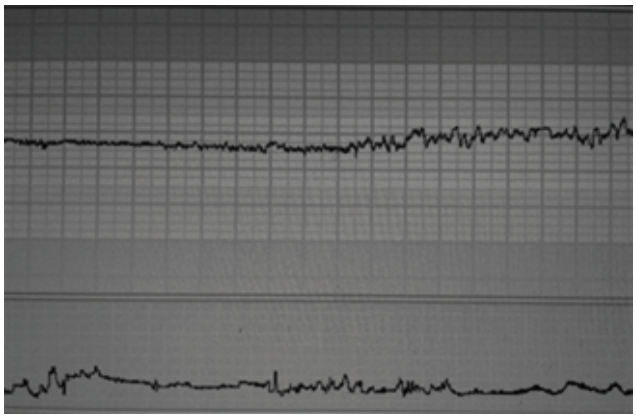

Figure 3: CTG of a fetus at 34 weeks of gestation: note baseline heart rate within the normal range, normal baseline variability with "cycling".

and fetal electrocardiograph (Fetal ECG or ST-Analyser) also cannot be used in this gestation. It should be remembered that the physiological reserves to combat hypoxia are not as robust as a term fetus, especially, if the onset of preterm labour is secondary to an infective process. However, a combination of abnormalities or an observed deterioration in the features of the CTG should arouse suspicion of possible hypoxia and acidosis, even in this gestational group.

4.3. 28–32 Weeks. With increasing gestation the baseline fetal heart rate is likely to decrease from the upper limits of the normal range. Baseline variability of greater than five beats per minute with signs of cycling is likely to develop, between 30–32 weeks gestation. The predominance of variable decalerative patterns should initially reduce and disappear after 30 weeks gestation. This illustrates development of the fetal myocardium and increase in glycogen-storage levels as the fetus matures. Persistence of late decelerations within this cohort is likely to represent ongoing uteroplacental insufficiency. In this situation, the blood flow within the intervillous space is decreased resulting in accumulation of carbon dioxide and hydrogen ion concentrations. In the noncompromised, nonacidaemic fetus, intermittent hypoxia results in decelerations with subsequent transient fetal hypertension [8]. With passage of time, continuation of this hypoxic insult will lead to acidaemia, loss of initial "compensatory" hypertensive response, and may proceed to cause permanent cerebral injury. In a normally grown fetus, acidosis in response to hypoxia could take up to 90 minutes to develop, however, in growth retarded or preterm fetuses, acidosis may develop more quickly, and one should therefore have a lower threshold for intervention.

Practice Points. Survival dramatically increases beyond 28 weeks as the fetal organs are relatively mature and there is significant improvement in fetal neurological development. Hence, fetal monitoring is recommended in this gestational group.

Table 2: Interpretation of fetal blood sample (FBS) results.

FBS result	Interpretation
>7.25	Normal FBS result
7.21–7.24	Borderline FBS result
<7.20	Abnormal FBS result

Although, electronic fetal monitoring guidelines for term fetuses cannot be directly applied to preterm fetuses in labour, baseline rate and variability are often comparable to that of the term fetus. Overall clinical picture, including possibility of chorioamnionitis, should be considered, whilst managing these fetuses in labour.

4.4. 32–34 Weeks. Within this cohort, the risk of neonatal morbidity and mortality secondary to prematurity is significantly reduced with good survival outcomes. Continuous fetal heart rate monitoring in this group is recommended, following agreement with the patient. Features of CTG classification into nonreassuring and reassuring (as outlined in Table 1) according to NICE guidelines could be considered. This is because physiological maturity of the cardiovascular system and the neural control of the fetal heart rate during this gestational period is similar to that of a term fetus (Figure 3).

Practice Points. Baseline fetal heart rate and variability should be comparable to the term fetus and accelerations with an amplitude of greater than 15 beats from the baseline should be present as an indicator of fetal well-being. Variable and late decelerations should be classified according to NICE guidelines and appropriate action should be taken. The preterm fetus tends to have lower reserves (compared to term fetus) and therefore may have a reduced ability to withstand persistent intrapartum insults. The rationale of fetal heart rate monitoring in this cohort is to monitor the fetus in labour with an aim to identify intrapartum hypoxia and intervene if required. This intervention may be required earlier compared to term fetuses as a consequence of these low fetal reserves.

5. Role of Additional Tests of Fetal Wellbeing in Monitoring a Preterm Fetus

Several additional tests of fetal well-being are used in labour, which include fetal blood sampling (FBS), fetal pulse oximetry, and fetal electrocardiograph (STAN analysis). These adjuvants to electronic fetal monitoring were introduced to reduce the false-positive rate associated with CTG monitoring [10]. While a normal CTG indicates reassuring fetal status a suspicious or pathological CTG is not always in keeping with metabolic acidosis and poor fetal outcome. The poor-positive predictive value of CTG in addition to variation in CTG interpretation can often lead to unnecessary intervention and high-operative delivery rates [11].

Table 3: Proposed Management Algorithm "ACUTE" for intrapartum fetal monitoring (CTG) in preterm gestations (<34 weeks).

A	Assess survival and long-term outcome at the *given* gestational age.
C	Consider the wider clinical picture:presence of co-existing infection, maternal age, condition of the fetus (severe growth restriction, congenital malformations), wishes of the woman (e.g., request to "do everything possible" in view of IVF conception, previous preterm losses) in formulating management plan.
U	Understand normal fetal cardiovascular and nervous system physiology at the *given* gestation in interpreting the CTG.
T	Treatment of underlying predisposing factors of uterine irritability (infection, antepartum haemorrhage) and treatment of preterm labour (tocolytics and steroids, if appropriate) to optimise maternal and fetal outcome.
E	Evaluate maternal risks of operative interventions (classical C. section, haemorrhage, infections, increased risk of uterine rupture in future pregnancies) and potential fetal benefits (survival and long-term morbidity) due to commencing continuous electronic fetal monitoring at the *given* gestation and counsel appropriately.

5.1. Fetal Blood Sampling. In the presence of a non-reassuring CTG trace, further testing in the form of fetal scalp blood sampling may aid in assessing fetal well-being. After rupture of membranes and once the cervix is adequately dilated (>3 cm), sampling a small amount of blood from the fetal scalp can be used to measure pH or lactate and thus detect acidosis. It is not recommended in fetuses with bleeding disorders and is contraindicated in pregnancies complicated with HIV, Hepatitis B or C as it may increase vertical transmission. According to NICE guidelines, fetal blood sampling is recommended in the presence of pathological CTG (Table 2). If the pH value is <7.20, immediate delivery is recommended, whereas a pH of 7.20–7.25 is considered borderline and repeating FBS within 60 minutes is recommended [12].

With regards to the pre-term fetus, fetal blood sampling has not been validated in this group. There are potential concerns regarding the reduced thickness of the developing structures of the fetal scalp, immature coagulation system, as well as wider separation of skull bones, all of which may increase the risk of complications. Moreover, studies have shown fetal acidosis to occur more often in pre-term fetuses delivered before 34 weeks than those delivered between 34–36 weeks [5]. Despite this high rate of fetal acidosis, the short-term fetal outcome was good and in subsequent repeat blood-sampling pH values had normalized [5]. This high rate of dramatic fetal acidosis in the preterm may represent an alternative intrapartum compensatory mechanism. Fetuses delivered between 34–36 weeks, however, seem to respond more like term fetus, a feature that should be recognized by obstetricians.

5.2. Fetal Pulse Oximetry. Fetal pulse oximetry was first introduced in clinical practice in the 1980s. It provided a means of monitoring fetal oxygen saturation of fetal haemoglobin that is measured optically (similar technology for pulse oximetry in adults) during labour. In non-reassuring CTG traces, pulse oximetry was initially felt to provide a more sophisticated way of detecting adverse neonatal outcome. Several studies defined a critical threshold of <30% SpO2 persisting for greater than ten minutes as a predictor of fetal acidosis and poor neonatal outcome [13]. This cut off value yielded a sensitivity of 81% and specificity of 100% to predict scalp pH of <7.2 [14]. Recent large RCT's, however, have demonstrated no reduction in operative delivery rate or in predicting adverse neonatal outcome [15]. This mode of fetal monitoring now remains obsolete and the manufacturers have ceased production.

5.3. Fetal ECG (ST Analyser or STAN). This technology is based on analyzing the ST segment of the fetal myocardium for ischaemic changes during fetal hypoxia as well as determining the ratio between the T wave and QRS complex (T/QRS Ratio) of the fetal ECG. The latter is altered secondary to release of potassium during glyocogenolysis in the fetal myocardium mediated through that catecholoamine surge, which occurs during hypoxic stress. Myocardium of a preterm fetus has less stored glycogen with increased water content and also the epicardial-endocardial interphase is much smaller than a term fetus. Hence, ST analyser is not recommended prior to 36 weeks of gestation as it may not be reliable due to changes in the myocardial composition described above.

5.4. Preterminal Trace. A fetus that demonstrates features of preterminal trace has exhausted all its reserves to combat hypoxia and hence immediate delivery is recommended [16]. However, caution should be exercised in fetuses prior to 28 weeks that demonstrate such features as perinatal outcome is poor in this group. Hence, a woman should be counseled that the risks of operative intervention may outweigh the benefits.

6. Conclusion

Continuous electronic fetal monitoring of preterm fetuses poses a clinical dilemma to clinicians caring for these fetuses during labour. Although, clinical evidence-based guidelines and recommendations exist for monitoring term fetuses during labour, there is paucity of scientific evidence in the preterm group. Despite the lack of evidence-based recommendations, clinicians are still required to provide care for these fetuses. Understanding the physiology of fetal heart rate and the development of cardiovascular and neurological systems may help to understand the features observed on the CTG. It is important to realize that physiological reserves available to combat hypoxia are less than those available to a term fetus. Hence, a preterm fetus may suffer a hypoxic insult sooner than its term counterpart. It is vital to counsel women prior to instituting continuous electronic

fetal monitoring, especially in extreme preterm fetuses (24–26 weeks) as survival in this group is largely determined by fetal maturity than the mode of delivery. In view of the absence of guidelines and recommendations monitoring preterm fetuses, we have produced a management algorithm "ACUTE" to aid continuous intrapartum fetal monitoring in fetuses prior to 34 weeks (Table 3). Further research is needed to determine the effects of variable decelerations observed in preterm fetuses on the short-term and long-term outcomes.

Conflict of Interests

The authors declare no conflict of interests.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2011, Article ID 980985, 6 pages
doi:10.1155/2011/980985

Research Article

Use of Near-Infrared Spectroscopic Analysis of Second Trimester Amniotic Fluid to Assess Preterm Births

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Received 4 April 2011; Accepted 21 June 2011

Academic Editor: Yves Jacquemyn

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This pilot study investigated the possibility that metabolomic differences exist in second trimester of women delivering at term (≥37 weeks, $n = 216$) and preterm (≤35 weeks, $n = 11$). For this retrospective study, biobanked AF samples underwent near-infrared (NIR) spectral analysis using wavelengths from 700 to 1050 nm. Spectral data was compressed then optimized by multilinear regression to create a calibration model. The resultant model was able to classify term and preterm births based on differing AF metabolomic profiles with a sensitivity and specificity of 100%. When groups were classified using a prematurity index (PI), there was a statistical difference ($P < 0.001$) between the predicted preterm group (PI 0.77 ± 0.08) and the term group (PI 1.00 ± 0.02). In conclusion, the 2nd trimester AF samples showed distinct differences in metabolomic profiles between patients delivering preterm as compared to those at term in functional groups related to proteins, carbohydrates, fats, polyols, and water.

1. Introduction

Preterm birth, defined as birth prior to 37 weeks of gestation, is a leading cause of infant morbidity and mortality worldwide [1] and has been increasing [2, 3]. Since 1990, the number of preterm births has risen by 20% [4] and is even more significant when the increased costs associated with preterm pregnancies are considered [5]. However, despite advances in identifying some of the causes of preterm birth [6], our understanding of the physiologic process leading to preterm labor is poorly understood [7].

A growing body of literature has been examining possible proteomic markers for preterm labor and for intrauterine infection, a leading cause of preterm labor [6], in maternal serum [8, 9] and in amniotic fluid [9, 10]. None has produced significant positive predictive value for preterm births. On the other hand, metabolomics, which is the summation of ongoing cellular activity and downstream of protein metabolism [9, 11], may provide another interesting approach.

Metabolomics is the measurement of multiple small molecules in various tissues and fluids. These small molecules are the products of protein metabolism and cellular function within an organism. When examined as a whole, these metabolites can be viewed as biomarkers of a functional phenotype [12]. In the case of preterm labor, differences in metabolomic profiles found in amniotic fluid are thought to be possible since biological processes of the fetus and the mother both impact on its biochemical composition.

One successful approach to measure metabolomic profiles uses near-infrared (NIR) spectroscopy. The use of NIR vibrational spectroscopy preserves the matrix of constituent metabolites and provides important information about the interactions among the various constituents in situ. This can provide insight into metabolism, based on relational properties that cannot be captured when individual components are measured. Metabolite profiling using NIR spectroscopy has been used to detect disease in different

Table 1: Population Demographics.

Maternal/Fetal Characteristics[a]	≤35 weeks	≥37 weeks	P
Gestational Age (wks)	34.8 ± 2.4*	39.3 ± 1.9	N/A
Maternal Age (yrs)	37.5 ± 1.7	37.6 ± 2.4	0.4
Pre-pregnancy BMI (kg/m^2)	23.8 ± 4.3	23.8 ± 4.9	0.6
Amniocentesis Week	15.5 ± 0.8†	15.2 ± 1.0‡	0.8
Birth weight (g)	2555 ± 540	3429 ± 623	<0.05
Parity	1.2 ± 0.6	1.1 ± 1.1	<0.05

[a]Data are reported as means ± standard deviation. Population characteristics for mothers delivering in term ($n = 216$) and preterm ($n = 11$). *Range is 28.5–35.1 weeks. †Range is 14–17 weeks. ‡Range is 12–20 weeks.

scenarios where discrimination between groups is an objective [13]. Specifically, the application of NIR spectroscopy to amniotic fluid has been used to predict fetal lung maturity [14, 15]. Differences in these metabolomic profiles obtained by NIR spectroscopy also employ multivariate regression models and optimization functions [16, 17].

This pilot study was undertaken to test the hypothesis, using NIR spectroscopy, that differences in the metabolomic profile exist in second trimester amniotic fluid samples for term (≥37 weeks) compared to preterm births (≤35 weeks). We propose that identifying the existence of a metabolic fingerprint for preterm labor early in pregnancy could be of major importance in the appropriate ongoing monitoring of at-risk pregnancies and the development of a better understanding of the biologic basis of preterm labor.

2. Materials and Methods

This was a retrospective cohort study, approved by both the McGill Institutional Review Board and St. Mary's Hospital Center (Montreal, Canada). The population included 227 subjects recruited between 2000 and 2003 who provided a small volume of amniotic fluid for spectral profiling using NIR. Women were subdivided into term and preterm categories. Inclusion criteria for term births ($N = 216$) included age-related amniocentesis for genetic testing and a singleton pregnancy with no fetal complications. The preterm group included only patients with premature rupture of members (PROM) and/or preterm labour and a spontaneous vaginal delivery; patients who were induced or had a C-section were excluded. Demographics of the study participants are listed in Table 1. The two study groups were similar with respect to both maternal age and maternal BMI. The AF samples were obtained following genetic testing and stored at −80°C; there is minimal source of biochemical error resulting from repeated freezing and thawing of amniotic fluid [18, 19].

To determine the feasibility of estimating true premature births using spectral analysis of 2nd trimester amniotic fluid collected at 12–20 wks gestation, a calibration model was constructed using a set of AF samples with known birth outcomes in the NIR region of the spectra (700–1050 nm). This spectral region is known to contain functional group information on overtone bands of CH, NH, and OH moieties [20]. Glucose, proteins, fatty acids, oils, and myoglobin have been identified as contributing to the absorbance in this NIR region [21–23].

Prior to analysis, frozen AF samples were thawed at room temperature (25°C) for 30 minutes. NIR profiles were analyzed using a reflective spectrograph with a CCD detector (B&W TEK, Newark, DE) in randomized order. A flow sample cell with 10 mm path length was filled with 15 μl of sample media. Spectra were recorded from 700–1050 nm at room temperature (25°C ± 1°C). The spectrophotometer was set to measure absorbance relative to air, and a signal average of 200 measurements with an integration time of 100 ms for each measurement was used. This measurement procedure involved rinsing the sample cell with 1 ml of 0.1 M NaOH followed by 5 ml of distilled, deionized water. The last injection of water was used to record a reference spectrum.

Quantification of the sample properties from NIR spectra consisted of determining the most parsimonious combination of variables in selected wavelength domains using a genetic algorithm optimization [16]. In this method preprocessing based on Haar wavelets, which is similar to jpeg compression of images, was used to objectively select wavelength regions. A combination of wavelength regions that most parsimoniously estimated prematurity index was determined by inverse least-squares regression, using a genetic algorithm optimization. The model investigated is of the form

$$Y = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \cdots + \alpha_n x_n, \quad (1)$$

where Y is the dependent variable or prematurity index (PI), $x_1, x_2, \ldots, x_n$ are independent variables (i.e., integrated wavelength region), and $\alpha_0, \alpha_1, \ldots, \alpha_n$ are the coefficients determined from a set of calibration x's. Many models were screened using the GA which is based on genetic principles such as mating, crossover, and mutation, to select the wavelength region that best separates the term and preterm groups [16].

Each sample was estimated independently using a leave-one-out cross-validation approach in a continuous multilinear model. For each individual in the population, the coefficients α_1 to α_n of (1) were calculated by inverse least-squares regression using an independent calibration. Estimates of prematurity index were obtained by applying (1) with the determined α_n parameters and the x-values of a monitoring set. Fitness of the model for each wavelength region selected was calculated as the squared difference between the mean of the term and preterm groups divided by the sum of the pooled variance. A higher fitness corresponds to better separation between the two groups as calculated by a Student's t-test. Subsequent to the estimated prematurity index (PI) optimization, notched box plots, Student's t-test results, and a receiver operator curve (ROC) were used to separately determine the statistical characteristics of the groups. The optimum value for the sensitivity and specificity was determined from the ROC [24, 25].

Additionally, spectra were examined using the major chemical groups present in the 700–1050 nm region of the NIR spectra. Molecular absorbance regions in the NIR related to H_2O, ROH, CH_2, and NH_3 were defined using

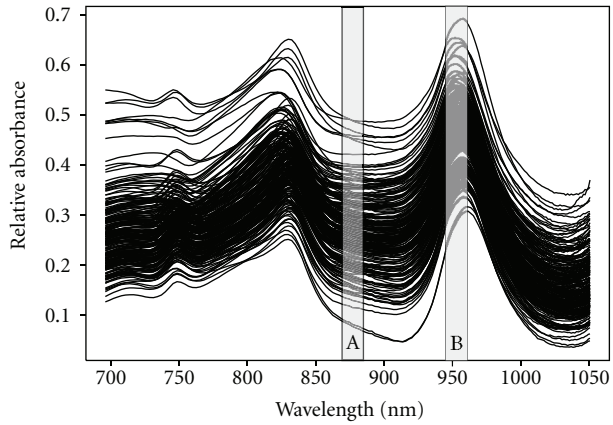

Figure 1: Raw data from 227 NIR spectral profiles of AF samples plotted relative to air. The boxes labeled A and B show the regions selected by a genetic algorithm, which give the best separation of term and preterm groups.

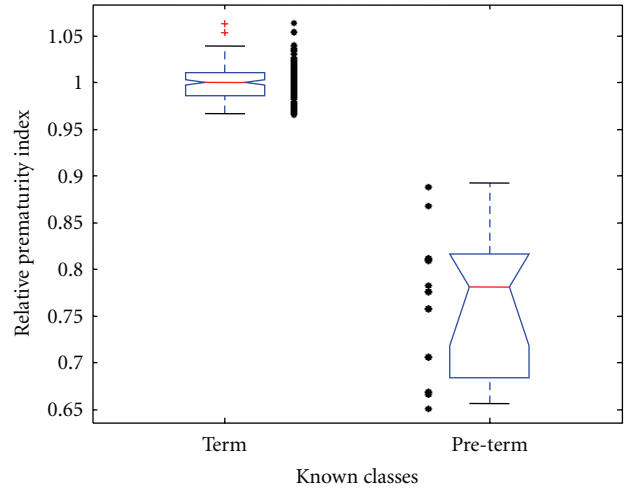

Figure 2: Box plots comparing the prematurity index for term and preterm births.

known standards [20]. Means and standard deviations were then calculated for normal (≥37 wks) and preterm (≤35 wks) using these integrated regions. Likewise, ratios of pairs of selected functional groups (NH_3/CH_2, NH_3/ROH, CH_2/ROH CH_2/ROH, NH_3/H_2O, and CH_2/H_2O) were determined to characterize concentration shifts in glucose, proteins fats and oils relative to water as well as polyols, which may play important roles in maintaining ATP concentrations, cellular redox potential, and in drawing water and solutes across the placenta [26].

All statistical analysis was done using the MATLAB (the Math Works Inc., MA) programming package.

3. Results

Population characteristics are described in Table 1. As expected, gestational age and birth weight differed. Figure 1 describes NIR spectral differences for each individual in the range of 700–1050 nm. Of all of the possible wavelet combinations, only two wavelet regions were needed to develop the best model to distinguish preterm from the term births. Those wavelet regions selected by the genetic algorithm were at 872–879 nm (region A) and 943–954 nm (region B), respectively. The first wavelength region corresponded to third overtone CH_3 and second overtone NH group vibrations [21]. This wavelet was negatively correlated with concentrations of chemicals absorbing in this region. Wavelet B selected an absorbance region characterized by aliphatic alcohol functional groups and third overtones from CH vibrations in the 943 to 954 nm wavelength range. These were negatively correlated with preterm births.

A parsimonious calibration model was constructed with the 2 wavelets selected by the genetic algorithm. Using these regions, the prematurity index (PI) was calculated. Each data point represented a blind estimation of the optimal separation value using the rest of the data for calibration. Results are represented in Figure 2 as notch box plots showing the statistical distribution for each group of classified samples [25]. A relative prematurity index (RPI) was calculated as a percentage of the median of the normals. The size of each box was determined by the quartile distribution about the median of the data. The median of the term group was 1.00 ± 0.02 and was 0.78 ± 0.08 for the preterm group. Notches of box plots, which do not overlap, have different medians at the 5% confidence level [25].

In addition, the mean and standard deviations of preterm and term prematurity indices were 0.77 ± 0.08 and 1.00 ± 0.02, respectively ($P < 0.001$). Table 2 summarizes the results of the model's validation. Using only the 2 components for the calibration model, AF samples were classified into preterm and term groups with 100% sensitivity and specificity determined by a ROC curve. Positive and negative predictive values were 100% (Table 2).

To further understand the relationship of the measured spectra to prematurity, differences in the amniotic fluid metabolomic profile between preterm and term infants arising from changes in selected spectral regions were examined. Regions selected for integration of the various functional groups as well as normalized spectra for the means for both the normal and preterm groups are shown in Figure 3. There were substantial metabolomic differences in the spectra between term and preterm infants. As well, ratios of the integrated signals from the different functional groups (Table 3) suggested nonsignificant trends in the concentrations of functional groups relative to water and/or polyols. There was a relative increase in concentration of protein as compared to carbohydrates and fats (NH/CH ratio) even though both decrease in total concentration as reflected in theNH/H_2O and CH/H_2O ratios. There was also nonsignificant increase in the NH/ROH ratio and a decrease in the CH/ROH ratio related to preterm births.

4. Discussion

Previous studies have shown gestational length is difficult to predict [9]. Genomics, proteomics, mass spectroscopy, and

Table 2: Results for the cross-validation of the calibration model and diagnostic statistics.

Preterm pregnancies		Control term pregnancies	
No. of group	11	No. of group	216
Prematurity index (PI) ($\bar{x} \pm$ sd)	0.77 ± 0.08*	Prematurity index ($\bar{x}s \pm$ sd)	1.00 ± 0.02
True positives	11	True negatives	216
False negatives	0	False positives	0
Sensitivity	100%	Specificity	100%
Positive predictive value	100%	Negative predictive value	100%

*P value < 0.001.

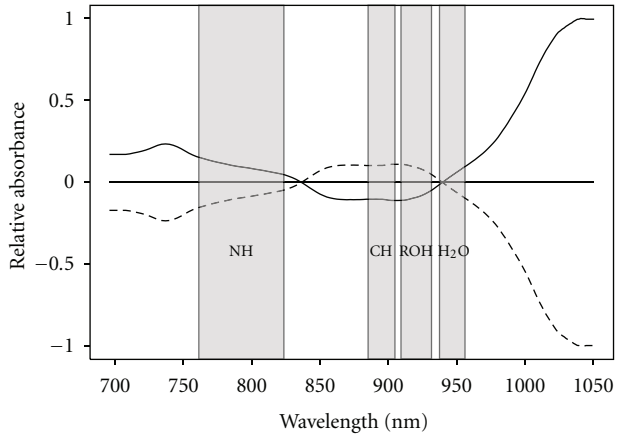

Figure 3: Normalized spectral absorbance for term and preterm groups. A solid line represents the term group (≥37 weeks), and the dashed line represents the pre-term group (≤35 weeks). This region of the spectrum consists of the 2nd and 3rd overtone absorption from CH, NH, and OH functional groups. Differing concentrations of proteins, fats, and carbohydrates in the matrix lead to increased or decreased absorbance in the spectral region corresponding to the functional groups. The result is essentially a metabolome fingerprint for preterm and term births using 2nd trimester amniotic fluid.

Table 3: Means and standard deviations by functional groups for term and preterm births[a].

Functional group ratios	Gestation period[b]	
	Preterm < 35 weeks[c]	Term ≥ 37 weeks
NH/CH*	3.49 ± 0.5	3.43 ± 0.8
NH/ROH†	2.38 ± 0.3	2.36 ± 0.4
CH/ROH‡	0.69 ± 0.0	0.69 ± 0.0
NH/H_2O§	2.28 ± 0.2	2.29 ± 0.2
CH/H_2O¶	0.67 ± 0.1	0.69 ± 0.1

[a]Data are reported as means ± standard deviation. Birth outcomes and second trimester amniotic fluid functional groups ratios for mothers delivering in term ($n = 216$) and preterm ($n = 10$).
[b]All the differences between term and preterm groups were nonsignificant at a confidence level of 10%, with the exception of NH/CH which had a P value of 0.090.
[c]It is important to mention that one sample that had a gestational age of 35.1 was discarded as an outlier. Its exclusion from this ratio analysis was primarily because it had a gestational age 2 weeks above the mean and also was 500 g heavier than the average of the group. *Relative amount of protein to carbohydrates/fats. †Relative amount of protein to modified polyalcohols. ‡Relative amount of carbohydrates/fats to modified polyalcohols. §Relative amount of protein to water. ¶Relative amount of carbohydrates/fats to water.

other assays have been used for analysis of maternal and fetal biofluids with poor success rates [8, 9, 14, 15]. In contrast, the results of this pilot study showed that NIR spectral waveforms differed significantly in the range 700–1050 nm between term and preterm births. Varying concentrations of several functional groups contributed to the variation in these spectral analyses, confirming our hypothesis that metabolomic differences exist early in pregnancy in the amniotic fluid of second trimester pregnancies between subjects delivering preterm and those delivering at term.

Although the spectral features are broad, absorbance is still directly related to the concentration of CH, NH, and OH functional groups within the matrix. These differences seen in the preterm group corresponded to CH_3 and NH (region A), aliphatic alcohols and CH functional groups (region B). Presence of proteins, water, and polyalcohols in AF are well known and can differ in concentration from sample to sample [26]. Our findings are intriguing in that they suggest the underlying processes ultimately leading to preterm delivery are present between 12 and 20 weeks of gestation. Prior studies have focused on identifying biomarkers present in amniotic fluid at the onset of preterm labor [8, 9, 14, 15]. Likewise, limitations such as AF samples taken after 22 weeks gestation, destructive analytical methods, and small populations plague many existing techniques [6, 9, 10, 14, 15]. Others have cited inability to distinguish preterm from term groups [10] and low positive predictive values [9].

Techniques from proteomics and genomics also have characterized few biomarkers in AF, thus limiting the amount of information about bioprocesses that might be associated with the amniotic fluid matrix [9–11]. The differing metabolomic profiles seen here in early pregnancy may represent an abnormal metabolic process in the fetus that ultimately predisposes the pregnancy to insults resulting in preterm labor and delivery. In addition, many recent technologies using proteomics and genomics rely on invasive procedures, expensive equipment, and technical expertise [6, 8–10]. The use of metabolomics with NIR spectroscopy is relatively inexpensive, easy to use and can characterized a metabolomic fingerprint resulting from multiple biological processes.

These results, however, should be considered preliminariy since the number of patients in the preterm delivery group is small. Despite this, our data using spectral analysis were able to distinguish between preterm and term deliveries with 100% sensitivity and specificity, which supports the potential diagnostic possibilities of this technique. Even though we were not able to identify specific differences in the ratios of the functional groups, probably owing to our small sample size, the strength of our results lies in the power of the spectral analysis to extract meaningful information about the metabolic profile from the 2nd trimester AF matrix that was associated with distinct metabolomic fingerprints early in pregnancy in our preterm and term deliveries. Moreover, the suggested metabolomic profiles were consistent with previous studies that show increased protein in amniotic fluid of premature infants [27], alterations in polyols in IUGR infants [26] and with a higher incidence of oligohydramnios [28].

Our results raise the question of whether obtaining metabolomic profiles of amniotic fluid in early pregnancy will help obstetricians identify those pregnancies destined to deliver preterm. Additionally, it may be possible to develop a noninvasive probe to analyze the NIR spectra of amniotic fluid on an ongoing basis. If future studies using larger sample sizes confirm these findings, this information would indicate that a "problematic metabolomic profile" emerges very early in pregnancy and could lead to much earlier identification of prematurity and earlier decision for potential therapies.

Conflict of Interests

None of the authors have any conflict of interests regarding this work.

Acknowledgments

The project was funded by grants from the Natural Science and Engineering Research Council of Canada and the Canadian Institute for Health Research. J. E. Sanchez-Galan thanks SENACYT and IFARHU, government agencies of the Republic of Panama, for sponsoring his Ph.D. studies at McGill University.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2011, Article ID 186560, 5 pages
doi:10.1155/2011/186560

Review Article

Review of the Recent Literature on the Mode of Delivery for Singleton Vertex Preterm Babies

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Received 26 March 2011; Accepted 26 May 2011

Academic Editor: Yves Jacquemyn

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Choosing the safest method of delivery and preventing preterm labour are obstetric challenges in reducing the number of preterm births and improving outcomes for mother and baby. Optimal route of delivery for preterm vertex neonates has been a controversial topic in the obstetric and neonatal community for decades and continues to be debated. We reviewed 22 studies, most of which have been published over the last five years with an aim to find answers to the clinical questions relevant to deciding the mode of delivery. Findings suggested that the neonatal outcome does not depend on the mode of delivery. Though Caesarean section rates are increasing for preterm births, it does not prevent neurodisability and cannot be recommended unless there are other obstetric indications to justify it. Therefore, clinical judgement of the obstetrician depending on the individual case still remains important in deciding the mode of delivery.

1. Introduction

Choosing the safest method of delivery and preventing preterm labour to reduce the number of preterm births and improve the outcomes for mother and baby is an obstetric challenge.

Optimal route of delivery for preterm vertex neonates has been a controversial topic in the obstetric and neonatal community for decades and continues to be debated. The value of Caesarean section in preterm labour is less clear [1, 2]. This has not been subjected to robust randomised controlled trial. The present evidence comprises of a number of case series, systematic review of controlled trials with variable results, from beneficial through equivocal to no benefit. Despite the uncertainty regarding benefits for preterm vertex neonates, cesarean section delivery rates have increased.

The aim of this paper is to review the recent literature to assess the effect of the mode of delivery on preterm vertex neonates. We present a series of questions and aim to find answers based on recent evidence.

2. Background

Preterm birth refers to the birth of a baby at less than 37 weeks of gestational age. Preterm birth is the major cause of neonatal mortality in the developed countries. In the UK, infant mortality among preterm births was 42/1000 live births in 2005, compared with 5/1000 live births overall [3].

Premature infants are at greater risk for short- and long-term complications, including disabilities and impediments in growth and mental development. Most mortality and morbidity affects very preterm infants (those born before 32 weeks of gestation) and especially extremely preterm infants (those born before 28 weeks of gestation). Late preterm birth (32 to 36 + 6 weeks of gestation) is associated with less risk than very preterm birth, but there is a growing recognition that even in this group there is increased risk of infant death [3]. The risk of death or neurosensory disability increases with decreasing gestational age [4].

The method of delivery is dependent on a variety of factors, and preterm labor per se does not dictate this one way or the other. Though the issue of how best to deliver is of importance to both obstetricians and neonatologists, there is little evidence from controlled studies on which to base the management of preterm birth. A Cochrane systematic review [2] commented that not enough studies have been done to provide adequate evidence.

Caesarean section has been postulated to have a theoretical advantage over vaginal delivery in premature infants.

This benefit may be the result of the avoidance of prolonged labour, allowing a less traumatic birth [5]. On the other hand, preterm Caesarean section can be technically difficult and may require performing a classical Caesarean section with adverse risks like scar dehiscence in future pregnancy [6]. It also has other maternal risks associated with Caesarean section. Hence, vaginal birth is the preferred mode in the absence of other obstetric indications due to reduced maternal complications. However, it involves the risk of hypoxia and future neurodisability to the baby. Balancing the fetal versus maternal risks and safety continues to pose challenges.

Therefore, we present the review of recent evidence to find out whether the decision-making process between obstetricians and neonatologists, regarding mode of delivery, can be made easier or if the debate continues leaving it on the clinical judgement of the obstetrician.

3. Discussion

3.1. Does Mode of Delivery Influence Neonatal Outcome in Preterm Births? New research suggests that the mode of delivery of very preterm infants whether vaginally or by Caesarean has little effect on neonatal outcomes. The findings come from a retrospective study unveiled at the American Congress of Obstetricians and Gynecologists 58th Annual Clinical Meeting in May 2010 [7]. This study included 126 preterm vertex singleton births with gestational age ranging from 23 to 30 weeks. The researchers compared outcomes that included neonatal deaths, intraventricular hemorrhage, necrotizing enterocolitis, respiratory distress syndrome, and clinical sepsis in 52 infants delivered by Caesarean and 74 delivered vaginally. Their conclusion was that mode of delivery does not provide any significant advantage in decreasing infant morbidity and mortality.

Similar findings came from a retrospective cohort study which was published recently [8]. They included all singleton deliveries occurring after spontaneous onset of labour between 25 + 0 and 32 + 6 weeks of gestation. 109 cases of spontaneous preterm labour were retrospectively selected, including 50 (45.8%) Caesarean sections and 59 (54.2%) vaginal deliveries. The neonatal outcomes compared between Caesarean and vaginal deliveries were perinatal death, cranial findings compatible with haemorrhage or white matter disease. The study concluded that in severely premature infants born after spontaneous onset of labour, the risk of adverse perinatal outcome does not seem to depend upon the mode of delivery.

Another study [9] included 124 preterm babies of higher gestations ranging from 30 to 35 weeks and compared the outcomes of 70 neonates born vaginally and 54 neonates born by Caesarean. Neonatal mortality rate was 20 percent for infants in Caesarean group as compared to 10 percent for vaginal group. There was no significant difference in the neonatal morbidity among both the groups.

Different to the above studies which were based on gestational age is one study [10] that assessed the survival advantage of premature newborns according to the mode of delivery based on birth weights (500–999 g, 1000–1499 g, 1500–1999 g, and 2000–2499 g). Overall Caesarean delivery rate in this group was 32.2%. Among preterm newborns with birth weight 500–999 g, 68 children were delivered vaginally and 5 by Caesarean section (5.7% and 0.4% of all preterm babies, resp.). None of the infants survived. The percentage of children from Caesarean deliveries in the other groups was higher: for preterm infants with birth weight 1000–1499 g—3.2%, 1500–1999 g—8.8%, and 2000–2499 g—19.8%. A survival advantage associated with Caesarean section was observed in neonates with birth weight 1000–1499 g ($P < 0.01$). On the basis of this study, it was concluded that Caesarean delivery is associated with a decreased neonatal mortality risk in preterm neonates only in those with birth weight of 1000–1499 g.

Based on the above studies, most agree that neonatal outcome does not depend upon the mode of delivery except one which found that Caesarean delivery could potentially reduce mortality in preterm neonates of birth weight of 1000–1499 g.

3.2. Does Caesarean Section Enhance the Survival Rate of Preterm Vertex Infants? Given the continuing debate about the benefits of Caesarean section for very preterm infants, MOSAIC (models of organising access to intensive care for very preterm babies in europe) project sought to describe Caesarean section rates for infants between 28 and 31 weeks of gestation ($n = 3310$) in ten European regions and their association with regional mortality and short-term morbidity [11]. There were no regional level correlations between Caesarean section rates and mortality and morbidity. The conclusion was that, with the exception of pregnancies with hypertension and growth restriction, there was broad variation in very preterm Caesarean section rates between regions after adjustment for clinical factors. It was suggested that given the maternal risks associated with Caesarean section, more research on its optimal use for very preterm deliveries is necessary.

Previous evidence comes from a Cochrane systematic review done in 2001 [2] which assessed the effects of a policy of elective Caesarean delivery versus selective Caesarean delivery (intention to deliver vaginally with recourse to Caesarean section) for women in preterm labour. Six randomized controlled trials with 122 women were included, and all trials reported recruiting difficulties. No significant differences between elective and selective policies for Caesarean delivery were found for fetal, neonatal, or maternal outcomes. Another publication of the same systematic review [1] found that odds of serious maternal morbidity were increased in the Caesarean section group (OR 6.2; 95% CI 1.3–30.1).

3.2.1. Evidence Supporting No Benefit of Caesarean Section on Survival Rate in Early and Very Low Birth Weight Preterm Births. An earlier published study [12] investigated the factors associated with Caesarean delivery and the relationship between mode of delivery and mortality in singleton vertex-presenting very low birth weight (< or = 1500 g)

live born infants. 2955 singleton vertex-presenting very low birth weight infants born at 24–34 were included. The primary outcome measure was mortality defined as death prior to discharge. Caesarean delivery rate was 51.7%. Caesarean delivery was directly associated with increasing maternal age and gestational age, small for gestational age infants, maternal hypertensive disorders, and antepartum haemorrhage and was inversely related to premature labour and prolonged rupture of membranes. Mortality rate prior to discharge was lower after Caesarean delivery (13.2% versus 21.8%), but in the multivariate analysis, adjusting for the other risk factors associated with mortality, delivery mode had no effect on infant survival (OR 1.00, 95% CI 0.74–1.33). This study concluded that Caesarean delivery did not enhance survival of vertex-presenting singleton very low birth weight babies.

Two other recent studies support this finding. The first was a retrospective cohort study [13] undertaken to compare neonatal outcome by method of delivery in very low birth weight less than 1500 g vertex-presenting fetuses. 2466 very low birth weight singleton liveborn vertex-presenting fetuses at less than 28 weeks were included, and analyses were stratified by birth weight, gestational age, and growth restriction to assess subgroup differences. This study found that Caesarean delivery offered no survival advantage to very low birth weight infants when compared with vaginal delivery. Survival benefit was noted for growth-restricted infants although only 12% of such infants delivered vaginally. The second study [14] done by the coauthor was also a retrospective study to evaluate the obstetric management and perinatal outcome of extreme prematurity (22–27 weeks) over a period of one year. A total of 57 babies were included and Caesarean section was the mode of delivery in 32%. Only 12.5% of babies delivered by Caesarean section at less than 27 weeks survived as compared with 70% survival rate at 27 weeks. Therefore, no survival advantage was noted among the babies delivered by Caesarean section below 26 weeks.

3.2.2. Evidence Supporting Benefit of Caesarean Section on Survival Rate of Early and Very Low Birth Weight Preterm Infants. Three studies provide evidence to support the above. First was a study [15] done in the United states which found that Caesarean section does seem to provide survival advantages for the most immature infants delivered at 22 to 25 weeks of gestation, independent of maternal risk factors for Caesarean section. Two other reports [16, 17] agreed to this finding and showed that survival advantage was associated with Caesarean delivery in the birth weight group of less than 1300 g.

Most of the above-mentioned studies included early preterm infants, but a study done in the United states [18] assessed the impact of Caesarean section on intermediate (32-33 weeks) and late (34–36 weeks) preterm births. The data suggested that for low-risk preterm infants at 32 to 36 weeks' gestation, independent of any reported risk factors, primary cesarean section may pose an increased risk of neonatal mortality and morbidity.

Therefore, recent evidence regarding this question is conflicting. Three studies [12–14] suggest that Caesarean section does not enhance survival of vertex-presenting singleton very low birth weight babies and cannot be routinely recommended unless there are other obstetric indications. Other three [15–17] have found Caesarean delivery to be beneficial in infants less than 26 weeks of gestation or birth weight less than 1300 g. Consideration though should also be given to the technical difficulty associated with Caesarean sections at earlier gestations which can increase maternal morbidity.

3.3. Is Caesarean Section Beneficial for Preventing Future Neurodisability in Very Low Birth Infants? Study from a district General Hospital in United Kingdom [19] included all infants weighing <1,250 g born between January 1995 and December 2003 and followed up at two years of age for assessment of the neurodevelopmental status by an independent paediatrician. 213 infants were analysed, of which 103 were born by vaginal delivery and 110 by Caesarean section They did not find any significant difference in the overall incidence of neurodisability in the infants born by Caesarean section as compared to those delivered vaginally. It was also noted that neurodisability was equally greater in babies with birth weight of 750 grams or less and/or born at 26 weeks or less gestation. Conclusion was that despite the increasing tendency to deliver extremely preterm babies by Caesarean, it was not associated with either reduced mortality or neurodisability at two years of age, and the method of delivery of very low birth weight premature infants should be based on obstetric or maternal indications rather than the perceived outcome of the baby. This is supported by another retrospective cohort study [20] which included a total of 1606 extremely low birth-weight infants (birth weight of 401–1000 g) who were born by cesarean delivery and 1273 could be followed up at 18 to 22 months of corrected age. They found that in extremely low birth-weight infants who were born by cesarean delivery, and after control for other risk factors, labor does not appear to play a significant role in adverse neonatal outcomes and neurodevelopmental impairment at 18 to 22 months of corrected age.

Similar findings came from another single-centre retrospective cohort study [21] of 84 cases of extremely low birth weight infants based on gestational age (below 28 weeks of gestation, 40% at or less than 25 weeks) performed in Italy. This study evaluated the impact of mode of delivery and timing of Caesarean section in extremely preterm births on long-term survival and psychomotor outcomes. Mortality and survival with neurological disabilities at 18 months of life were considered outcome measures. They found that mode of delivery and labour seem not to play a significant role in adverse neonatal outcomes, either mortality or neurodevelopmental impairment, in extremely low birth weight infants.

Two other studies [22, 23] investigated the association between the mode of delivery and intraventricular haemorrhage (IVH) in preterm infants. In the recent study [22] done which included infants with gestational age less than or equal to 28 weeks, Caesarean delivery was found to

decrease the risk of developing IVH in extremely preterm infants including the most severe grades of IVH. This is contradictory to the finding from a previous study [23] which investigated the association between delivery mode and grade 3-4 intraventricular hemorrhage in singleton, vertex presenting, very low birth weight (1,500 g or less) liveborn infants. They found that odds for severe intraventricular hemorrhage were not influenced by the mode of delivery in vertex-presenting singleton very low birth infants after controlling for gestational age.

To summarize, recent evidence suggests that Caesarean section could decrease the risk of severe IVH in extremely preterm infants but does not reduce future neurodisability.

3.4. Is Vaginal Delivery Safe? Vaginal delivery of preterm infant is associated with less maternal morbidity than caesarean section. The impact of vaginal delivery on 397 premature infants (44% born vaginally) weighing less than 1251 g was explored in one of the studies [24]. Outcomes measured were death, severe IVH, and periventricular leukomalacia (PVL). This study found that vaginal delivery was associated with higher risk of PVL. In infants weighing less than 751 g delivered vaginally, severe IVH is higher though the negative impact of vaginal delivery mode decreases as birth weight category increases.

Another study [25] which included 2,094 live births of infants at 23 + 0 to 27 + 6 of weeks gestation found that for preterm vertex without any other obstetric complications, 4 out of 5 infants were delivered vaginally without any increase in the risk.

Most of the other studies described in the earlier sections have not shown any difference in the neonatal outcome when vaginal and Caesarean deliveries were compared.

In summary, vaginal delivery can be associated with increased risk of IVH in very low birth weight infants, but no difference in the neonatal outcome and future neurodisability has been shown in most of the studies when compared to Caesarean section. Therefore it is reasonable to consider vaginal delivery safe in light of the accumulated evidence.

4. Conclusion

Effective care cannot be based on meta-analysis of well-designed controlled trials because none of the attempts have come to a conclusion. Recent findings from a number of studies have demonstrated that the neonatal outcome does not depend on the mode of delivery. Though Caesarean section rates are increasing for preterm births, there is conflicting evidence regarding its benefits in increasing the survival rate for early and very low birth weight preterm births. Moreover, it does not prevent neurodisability and cannot be recommended in light of recent evidence unless there are other obstetric indications to justify it. Future randomized controlled trials are necessary to support this recommendation which would be helpful in reducing the Caesarean section rates for preterm births.

It is important to consider the obstetric history, likely interval between induction and delivery in the context of deterioration of maternal health, probability of achieving a vaginal delivery compared to a risk of emergency section, presentation, and prelabour condition of the fetus. Hence, depending on the individual case, clinical judgment of the obstetrician still remains important in deciding the mode of delivery.

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Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2011, Article ID 286483, 4 pages
doi:10.1155/2011/286483

Research Article

The Influence of Prior Obstetrical History on Current 17-Hydroxyprogesterone Caproate Use

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Received 1 March 2011; Accepted 12 May 2011

Academic Editor: Jerome Cornette

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Objective. To determine if gestational age of prior preterm delivery influences a woman's receipt of 17-hydroxyprogesterone caproate (17-OHP-C). *Methods*. Retrospective cohort of women eligible for 17-OHP-C at Duke Obstetrics Clinic were identified by medical record review. Sociodemographic and clinical characteristics were abstracted. *Results*. Of 104 eligible subjects, 82 (78.8%) were offered 17-OHP-C. Of these, thirty-four (41.5%) declined. The median gestational age of the most recent preterm delivery was significantly lower among subjects who accepted 17-OHP-C as compared to those who declined (28.7 vs. 34.0 weeks, $P = .02$) and in subjects offered 17-OHP-C compared to those not offered 17-OHP-C (30.2 vs. 36.0 weeks, $P = .03$). Subjects not offered 17-OHP-C were more likely to have had an interval term delivery (31.8% vs. 9.7%, $P = .009$) *Conclusion*. Women with earlier preterm deliveries were more likely to be offered and accept 17-OHP-C. Prior obstetric history may influence both providers' and patients' willingness to discuss and/or accept 17-OHP-C.

1. Introduction

Preterm birth, defined as delivery prior to 37-week gestation, is the second leading cause of infant mortality in the United States after congenital malformations [1]. The incidence of preterm delivery continues to increase in this country such that it now exceeds 12% of all births [2]. The total national cost of care for premature babies is in excess of $13.6 billion annually [3]. Among survivors, the prevalence of both short, and long-term morbidities, including respiratory disease, neurodevelopmental problems, and gastrointestinal disease, is estimated to be as high as 60% [4].

The true cost of prematurity is only beginning to be understood. A recent study by Swamy et al. found diminished long-term survival and reproduction rates among individuals born prematurely in Norway between 1967 and 1988 [5]. It is becoming clear that, even if preterm infants surpass immediate obstacles, their overall long-term health is diminished. Despite extensive research in this field, the rate of preterm birth in the United States has increased over 20% in the past 20 years [2].

Recent randomized control trials have evaluated the role of 17-hydroxyprogesterone caproate (17-OHP-C) and progesterone gel or suppositories in the prevention of recurrent preterm birth [6–8]. Results from two trials suggest that administration of progestin to women at high-risk for preterm birth may decrease the recurrence risk by up to 35% [6, 7]. A more recent trial of progesterone vaginal gel versus placebo was not able to demonstrate a difference in the frequency of recurrent preterm birth ≤32 weeks in a high risk group of women [8]. The American College of Obstetricians and Gynecologists recommends that women at risk for recurrent preterm birth be considered candidates for progestin supplementation [9].

In a randomized trial of 17-OHP-C, Meis et al. found a preterm delivery rate with placebo of 55% much higher than the 37% that was originally predicted [7]. One proposed explanation for this finding was that the subjects enrolled in

the trial might have been at particularly high risk for preterm delivery and not necessarily representative of the general population of women considered eligible for 17-OHP-C. Perhaps women with histories of earlier preterm deliveries would be more likely to enroll in a trial of progesterone.

The primary objective in this study was to determine if gestational age of a prior preterm delivery influences *providers*' decisions to offer and *patients*' decisions to accept 17-hydroxyprogesterone caproate in the current gestation.

2. Materials and Methods

We conducted a retrospective cohort study of women eligible for 17-OHP-C at the Duke University Outpatient Obstetrics Clinic from January 2007 through June 2008. Approval was obtained from the Duke University Institutional Review Board. Subjects were identified by searching two independent obstetrics electronic clinical databases, and data were collected by chart abstraction.

All included subjects were pregnant and had a documented prior spontaneous, singleton preterm delivery due to either preterm labor or preterm premature rupture of membranes of less than 37 but more than 20-week gestation. Women with a multifetal gestation in the current pregnancy or with prior indicated preterm delivery were excluded from this analysis. Demographic and clinical characteristics collected include prior obstetric history, marital status, race, socioeconomic variables, pregnancy complications (preterm labor, gestational diabetes, abruption, antepartum bleeding, oligohydramnios, preeclampsia, gestational hypertension, or cerclage placement), pregnancy outcome, delivery route, chorioamnionitis, and indication for delivery. Neonatal outcomes collected included birth weight, sex, one- and five-minute APGAR scores, and congenital anomalies. If intermediate or intensive care was required, any further neonatal complications were recorded. The protocol at our institution is for the nurses to screen for 17-OHP-C eligibility and for the provider to enter into the electronic medical record if 17-OHP-C is offered. Patients with a prior history of indicated preterm delivery (such as for preeclampsia) were not eligible for 17-OHP-C at our institution and thus not included in this analysis. At our instituation, 17-OHP-C is started between 16/0 and 21/6 weeks and continues weekly until 34 weeks of gestation. We do not have a standard method for assessing compliance with progesterone therapy. Results were analyzed using t-test or Mann-Whitney for continuous variables and Fisher's exact test for categorical variables (Analyse-It, England, UK). For our primary objective, there were no missing data. Among the entire cohort, delivery data was unavailable for four patients (3.8%).

3. Results

Between January 2007 and June 2008, 104 subjects met eligibility criteria for 17-OHP-C. During the study period, approximately 1100 obstetrical patients were cared for in our clinical practice by twenty providers. Of the 104 eligible subjects, 82 (78.8%) were offered 17-OHP-C. Table 1 describes the demographic and clinical characteristics of women eligible for 17-OHP-C. Those women offered 17-OHP-C were significantly younger and less educated than those women not offered 17-OHP-C, but otherwise the two groups did not differ in demographic or clinical characteristics.

Among subjects eligible for 17-OHP-C, the median gestational age of the most recent preterm delivery was significantly lower for subjects offered 17-OHP-C as compared to those who were not offered 17-OHP-C (30.2 vs. 36.0 weeks, $P = .03$). In addition, subjects not offered 17-OHP-C were more likely to have had an interval term delivery, defined as a term delivery occurring after the index preterm delivery that qualified them for 17-OHP-C (31.8% vs. 9.7%, $P = .009$).

Table 2 describes the characteristics of women who were offered 17-OHP-C. Of the 82 subjects offered 17-OHP-C, 48 (58.5%) accepted treatment. Subjects that accepted 17-OHP-C had a lower median gestational age in their most recent delivery as compared to those who declined (28.7 vs. 34.0 weeks, $P = .02$). The median gestational age of the earliest preterm delivery (that with the lowest gestational age) was also lower among subjects that accepted 17-OHP-C as compared to those who declined although this did not reach statistical significance (28.0 vs. 32.0 weeks, $P = .11$). In addition, subjects who declined 17-OHP-C tended to be more likely to have had an interval term delivery as compared to those who accepted (17.6% vs. 4.2%, $P = .10$). There was no significant difference in the median gestational age at delivery in the current gestation between subjects who received 17-OHP-C as compared to those who did not (37.0 vs. 37.2 weeks, $P = .39$).

4. Discussion

Our primary objective was to determine if gestational age at a prior preterm delivery impacts a provider decision to offer and/or a patient decision to accept 17-OHP-C. In this study, the median gestational age of the most recent preterm delivery was 6 weeks earlier in subjects offered 17-OHP-C as compared to those not offered 17-OHP-C and over 5 weeks earlier in subjects who accepted 17-OHP-C as compared to those who declined. These findings suggest that a woman pregnancy history seems to influence both providers and patients offered 17-OHP-C and whether the treatment is accepted.

Despite the current enthusiasm for 17-hydroxyprogesterone caproate, few randomized trials have compared intramuscular progesterone or progestin to placebo for the prevention of preterm birth [7, 10–12]. In 1975, Johnson et al. provided some of the first evidence of an effect of 17-OHP-C on the prevention of recurrent preterm birth [11]. In 2003, Meis et al. found a reduction in the risk of preterm birth less than 37 weeks with the use of intramuscular 17-OHP-C among women at high risk for preterm delivery, but there was an unexpectedly high rate of preterm delivery in the place boarm [7]. This led to speculation that women enrolled in this trial were in some way at higher risk for recurrent preterm delivery than an average cohort of women with a history of preterm delivery. More complete demographics and pregnancy history of the patient group

Table 1: Demographic and clinical characteristics of subjects eligible for 17- Hydroxyprogesterone caproate (17-OHP-C).

Patient characteristic	Offered 17-OHP-C ($n = 82$)	Not offered 17-OHP-C ($n = 22$)	P value
Maternal age (mean years ± SD)	**27.6 ± 5.2**	**31.7 ± 6.3**	**.002**
% African-American	59.7 (49/82)	72.7 (16/22)	.26
% Single	63.4 (52/82)	59.1 (13/22)	.71
% Medicaid insurance	73.2 (60/82)	54.5 (12/22)	.09
Years of school ≤12	**64.4** (47/73)	**40.9** (9/22)	**.04**
Preeclampsia or gestational hypertension	17.5 (14/80)	27.3 (6/22)	.31
Cerclage (all types)	12.3 (10/81)	9.1 (2/22)	1.00
Multiple (>1) prior preterm birth	39.0 (32/82)	27.3 (6/22)	.31
Etiology of index preterm birth due to preterm labor	58.0 (47/81)	59.1 (13/22)	.93
Interval term delivery since preterm birth	**9.7** (8/82)	**31.8** (7/22)	**.009**
Cesarean section (current pregnancy)	25.6 (20/78)	9.1 (2/22)	.14
Birth weight (mean gm ± SD)	2662.9 ± 744	2653.6 ± 923	.96
Gestational age of most recent preterm delivery*	**30.2** (26.0–34.4)	**36.0** (27.5–38.0)	**.03**
Gestational age of earliest preterm delivery*	29.2 (25.0–33.0)	31.5 (24.9–36.0)	.20
Gestational age at delivery of current gestation*	37.0 (35.2–39.1)	37.9 (36.5–39.0)	.87

* Data presented as median and IQR.

Table 2: Demographic and clinical characteristics of subjects offered 17-Hydroxyprogesterone caproate (17-OHP-C).

Patient characteristic	Received 17-OHP-C ($n = 48$)	Declined 17-OHP-C ($n = 34$)	P value
Maternal age (mean years ± SD)	27.7 ± 4.8	27.5 ± 5.8	.87
% African-American	54.2 (26/48)	67.6 (23/34)	.22
% Single	64.6 (31/48)	61.8 (21/34)	.79
% Medicaid Insurance	77.1 (37/48)	67.6 (23/34)	.34
% Years school ≤12	60.4 (26/43)	70.0 (21/30)	.40
% Preeclampsia or gestational hypertension (current pregnancy)	19.6 (9/46)	14.7 (5/34)	.76
% Cerclage (all types)	12.7 (6/47)	11.7 (4/34)	1.00
Multiple (>1) prior PTB	37.5 (18/48)	41.2 (14/34)	.74
Etiology of index preterm birth due to preterm labor	55.3 (26/47)	61.8 (21/34)	.56
Interval term delivery since preterm birth	4.2 (2/48)	17.6 (6/34)	.10
Cesarean section (current pregnancy)	28.3 (13/46)	21.9 (7/32)	.53
Birth weight (mean gm ± SD)	2571 ± 836	2595 ± 558	.47
Gestational age of most recent preterm delivery*	**28.7** (25.3–32.8)	**34.0** (28.3–36.0)	**.02**
Gestational age of earliest preterm delivery*	28.0 (24.3–32.0)*	32.0 (25.2–34.0)*	.11
Gestational age at delivery of current gestation*	37.0 (35.2–38.4)*	37.2 (35.2–39.2)*	.39

*Data presented as median and IQR.

who refused randomization could help clarify the external validity of the Meis trial.

A more recent randomized trial by O′Brien investigated vaginal progesterone for the prevention of preterm birth in a group of 659 women. This large study failed to find a difference between the placebo and study groups [8]. This was in contrast to an earlier trial by da Fonseca showing a decrease in preterm birth rate from 28.5% to 13.8% in the vaginal progesterone group versus placebo [6].

The purpose of our investigation was to examine the population of women potentially eligible for 17-OHP-C at our academic institution. In our clinical practice, there seems to be a subset of higher-risk women that are preferentially offered and more likely to accept 17-OHP-C. We believe our study population is representative of the population of women with prior preterm deliveries seen in many academic practices. As this population is predominantly single, African-American and on Medicaid, we believe this is a population of women at high risk for recurrent preterm birth. Compared to other studies, we had fairly broad inclusion criteria, which makes our study more generalizable to different populations. As with any retrospective study, our study is limited only to the patients captured via our medical record search. In addition, our study is not designed

to evaluate the efficacy of 17-OHP-C. Other potential weaknesses include patient reporting bias on gestational age at prior preterm delivery. It is also possible that some patients were actually offered 17-OHP-C, but this was not documented. We did not assess for patient compliance with 17-OHP-C, which may be important in determining pregnancy outcomes.

The limited rate of 17-OHP-C utilization in our institution could have many etiologies. These could include system errors in implementation of 17-OHP-C for appropriate patients. However, a reliable system already exists at our institution for indentifying potential candidates. Rather, the low utilization among this population more likely relates to either patient perception of the utility or risks of the drug and/or disagreement with the recommendations on drug implementation among providers. This study did not evaluate patient or provider motivations for drug utilization.

Future research efforts are needed to determine the effect of patient and provider biases on the overall efficacy of 17-OHP-C. Studies could be directed at determining if there is a specific clinical phenotype that would benefit most from 17-OHP-C. Results in the literature are still mixed. In our study, 17-OHP-C was not commonly offered to women with a history of late preterm delivery. However, emerging evidence suggests that late preterm delivery causes greater morbidity than previously thought [13–15]. Although many providers do not offer 17-OHP-C to this group of women, it will be important not only to evaluate the effectiveness of 17-OHP-C in preventing recurrent preterm birth, but also to evaluate for a reduction of neonatal morbidity. Until these results are available, there will likely continue to be a bias among providers and patients with regards to offering and accepting progesterone supplementation.

Disclosure

This work was presented at the annual meeting for the Society for Maternal Fetal Medicine, January 31, 2009, San Diego, Calif, USA.

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