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In vitro myometrial contractility profiles of different pharmacological agents used for induction of labor

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Abstract

Objective—To investigate the effects of different pharmacological induction agents on myometrial contractility.

Study Design—Myometrial biopsies were obtained from 13 term non-laboring women undergoing scheduled cesarean delivery. Tissue strips were suspended in organ chambers for isometric tension recording. The effects of cumulative doses (10^{-10} M to 10^{-5} M) of Prostaglandin E1 (PGE1), E2 (PGE2) and oxytocin on spontaneous uterine contractility were determined. Areas under the contraction curve were compared using one-way ANOVA on Ranks with Dunn's post-hoc test.

Results—Oxytocin induced myometrial contractility was superior to PGE1, PGE2 and time controls (CTR) at all the concentrations tested. When only prostaglandins were compared to CTR, PGE1 10^{-5} mol/l increased myometrial contractility, while PGE2 had no effects.

Conclusion—Oxytocin and PGs have different effects on myometrial contractility accounting for different mechanisms of action and side effects. The increased uterine contractility observed with PGE1 as compared to PGE2 can contribute to explain the higher success of vaginal delivery.

Keywords

Prostaglandin E1; Prostaglandin E2; oxytocin; uterine contractility; organ chamber

INTRODUCTION

Induction of labor is the intentional initiation of labor before its spontaneous onset, when the risks to the mother and/or the fetus with pregnancy continuation outweigh the risks related to the intervention (1). Labor induction is one of the most frequent procedures in pregnant women, as in the United States it currently accounts for more than 20% of all deliveries (1, 2).

Normal labor depends on efficient myometrial contractions to efface and dilate a compliant cervix; therefore, methods of labor induction take into account both the uterus and the cervix (3). As the unfavorable cervix is a major impediment for the success of vaginal delivery (4), various pharmacological agents have been developed to achieve cervical ripening (1, 5, 6). Amongst them, Misoprostol (Prostaglandin E1, PGE1) and Dinoprostone (Prostaglandin E2,

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PGE₂) induce remodeling of the cervical extracellular matrix (7 - 9); oxytocin instead causes contractions that repeatedly press the fetal head against the cervix, and thereby contribute to cervical thinning (10). Additionally, not only oxytocin, but also PGE₁ and PGE₂ are thought to enhance myometrial contractility, as these agents have been shown to decrease the need for oxytocin augmentation of labor (11, 12)

The animate debate on which is the ideal pharmacological agent to use for induction of labor is still open to discussion. In fact, the American Congress of Obstetricians and Gynecologists acknowledges that oxytocin is still one of the most commonly used drugs independently of women's Bishop score (1). When used for cervical ripening, misoprostol resulted in longer interval to active labor and delivery compared with oxytocin according to Fonseca et al (13). On the other hand, a meta-analysis of the clinical trials not including the work of Fonseca et al demonstrated less vaginal deliveries within 24 hrs and more cesarean sections in the oxytocin group, as compared to the group receiving prostaglandins (PGs) (14).

Increased uterine contractions are observed during labor induction with both oxytocin and PGs; although extensive literature has focused on how contractions derive from oxytocin binding specific myometrial receptors (15), studies investigating the effects of PGs, especially Misoprostol, on human myometrial contractility in term pregnancy are lacking. Therefore, in this study we sought to compare in vitro myometrial contractility measured during incubation with oxytocin to the response induced by PGE₁ and PGE₂, using tissues collected from term pregnancies undergoing scheduled repeat cesarean delivery (CD), in order to better understand the mechanism of action, and possibly some of the side effects of such induction agents.

MATERIALS AND METHODS

The study was approved by the institutional review board of the University of Texas Medical Branch. Patients undergoing scheduled repeat cesarean section at term gestation (38-41 weeks) between May 1st and July 31st 2010 were approached for consent. Exclusion criteria were presence of more than 3 contractions per hour, rupture of membranes, placenta previa, and uterine conditions/abnormalities affecting contractility (such as leiomyomas).

In consenting women, 2×2×4 cm biopsies were taken from the upper edge of the transverse incision in the lower uterine segment, placed in Hanks' balanced salt solution (HBSS; Gibco BRL Products, Rockville, MD, USA), and transported to the lab. The biopsies were then prepared into 9×2×2 mm strips suspended in organ chambers for isometric tension recording.

Tissue organ chamber

Myometrial strips were mounted vertically in 10 mL organ chambers containing Krebs-Henseleit solution and prepared for isometric tension recording using stainless steel hooks and surgical silk sutures. One end of the strip was attached to a fixed support at the bottom of the chamber, while the other end was connected to an isometric force transducer. The temperature in the organ bath was maintained at 37°C and the solution was continuously bubbled with 5% CO₂ in air (pH ~7.4). Strips were equilibrated at the passive tension of 1g in Krebs' solution. Isometric tension was measured with Harvard isometric force transducers (Harvard Apparatus, South Natick, MA, USA) connected to a computer. The data were acquired and analyzed using Windaq data acquisition system (Dataq Instruments, Inc., Akron, OH, USA). The specimens were equilibrated for 1 – 2 hours until the contractions generated from passive tension application stabilized (contraction stabilization). The bath solution was changed every 30 min to maintain myometrial viability. Tissues with poor

spontaneous contractile activity were discarded with the assumption that they represented scar tissue or that the tissue was not viable at the time of the experiment. Cumulative concentrations (10^{-10} to 10^{-5} mol/l) of PGE1, PGE2, and oxytocin were then added. The area under the curve (AUC) defining myometrial contractions (integral activity) over a 25 min period was used as a measure of contractility. Baseline activity was defined as the integral activity over the 25 min following stabilization of spontaneous myometrial contractions. The effects of PGE1, PGE2 and oxytocin were expressed as percentage of the baseline activity, dividing the integral activity calculated after adding each dose of the agents by the baseline myometrial contractility. Temporal controls (CTR), were exposed to distilled water and used to normalize for the effects of time-dependent decay in contractility. Dose-response curves were then generated for PGE1, PGE2 and oxytocin, and for each the area under the curve (AUC) was calculated using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA, USA).

Drugs and Solutions

Dinoprostone and Oxytocin (Sigma, St Louis, MO, USA) were dissolved and diluted in distilled water, while Misoprostol (Sigma, St Louis, MO, USA) was dissolved in ethanol and then diluted in Krebs' solution. Stock solutions were aliquoted, kept at -20°C , and sonicated for 5 min to aid solubilization immediately prior to use.

Data analysis

Data were expressed as median and interquartile range [IQR]. Kruskals–Wallis analysis of variance on ranks followed Dunn's post hoc test was used to compare the different groups. Two-sided p value < 0.05 was considered statistically significant.

RESULTS

Uterine biopsies from 13 patients were included in the analysis. The demographic characteristics of the study participants are displayed in table 1. After discarding the samples with poor contractile activity or inadequate tension recording ($n = 24$), myometrial contractility was recorded in 28, 29, and 16 tissue strips respectively exposed to PGE1, PGE2 and oxytocin, as well as in 26 time control specimens. The median [IQR] of the tissue strips collected from each patient and tested with PGE1, PGE2 or oxytocin was 2 [2 – 2.25], 2 [2 – 2.25], and 1 [1 – 1] respectively. The median of the myometrial samples derived from each patient and used as time controls was 2 [2 – 3]. There were no statistically significant differences in baseline contractility between the study groups ($P = 0.3$) (figure 1). Myometrial contractility was significantly higher when myometrial samples were incubated with oxytocin as compared to PGE1, PGE2 and CTR ($p < 0.05$) at all the concentrations tested (figure 2). When comparing exposure to PGs to CTR, uterine contractility remained higher after addition of the maximal dose of PGE1 ($p < 0.05$; PGE1 10^{-5} mol/l vs CTR: 89.7 [64.3 – 134.2] % vs 62.1 [47.5 vs 81.4] %). PGE2 did not have any effect on uterine contractility at any concentration (figure 3).

CONCLUSIONS

We investigated the myometrial response induced by different pharmacological agents used for labor induction to better understand their mechanism of action and side effects: using myometrial biopsies from women at term undergoing scheduled repeat CD we found that myometrial contractility induced by oxytocin is far superior to PGs' ($p < 0.05$).

With the exception of the work from Fonseca et al (13), clinical trials have demonstrated that when compared to oxytocin infusion, PGs improve the chance of vaginal delivery

within 24 hours and reduce cesarean section rates (14). The discrepancy between in vitro data and clinical findings may suggest that in the event of an unfavorable cervix the intensity of uterine contractions may not be as relevant as cervical ripening to increase the chances of vaginal delivery. Prostaglandin E1 and E2 are also thought to enhance myometrial contractility, as they have been shown to decrease the need for oxytocin augmentation of labor (11, 12). In fact, their role in labor induction may involve various targets, creating a complex interplay between the uterine cervix and the myometrium, where increased uterine contractility may represent an indirect response to cervical ripening.

When the effects of PGs were compared to time controls, the only difference was detected after administering PGE1 10^{-5} mol/l, that significantly increased uterine contractions ($p < 0.05$). Both contractile and relaxant responses have been reported in myometrial samples from non-pregnant women exposed to PGE2 (16). When compared to controls, treatment with PGE2 10^{-5} mol/l and 10^{-6} mol/l resulted in relaxation of myometrial samples collected from term pregnancies at the time of CD (17, 18), although no consistent changes in contractility was observed at the same PGE2 concentrations when longer study intervals (30 min vs 10 min) were used (19). Moreover, studies conducted on pregnant women showed that serum PGE2 levels during labor were in the 10^{-8} to 10^{-9} mol/l range (20, 21), while we did not document any effect on myometrial contractility at higher PGE2 concentrations. Our results are consistent with the findings of Gordon Wright et al, indicating that high concentrations (10^{-5} mol/l, 10^{-6} mol/l) of PGE2 may induce a transient decrease in uterine contractility, or no changes at all, and that the initiation of uterine contractions observed during PGE2 labor induction may represent an indirect response to cervical ripening rather than a direct myometrial effect. Moreover, our work confirmed the findings of other authors that demonstrated greater in vitro myometrial contractility with oxytocin as compared to PGE2 in specimens collected from term pregnancies (17, 22). Instead, the increased in vitro uterine contractility observed with PGE1 at 10^{-5} mol/l as compared to PGE2 and time controls may contribute to explain the higher success of labor induction observed with Misoprostol as opposed to Dinoprostone (23).

Our data can also contribute to understand the role of uterine contractility in the etiology of complications from labor induction such as tachysystole. Tachysystole is defined as more than five contractions in 10 min, averaged over a 30-minute window (ACOG 2010 FHR tracings). If it occurs with a Category II or III tracing, intrauterine resuscitations should be initiated with discontinuation of uterotonics, and administration of tocolytic medications (eg. terbutaline) (24). Although in vitro myometrial contractility induced by oxytocin is far superior to the contractile response caused by PGs, tachysystole is more strongly associated with PGs (1, 12), indicating that such induction agents may indirectly affect uterine contractions through cervical ripening. The strengths of our study include selection of a homogeneous study population that consisted of non laboring women with term pregnancies undergoing scheduled repeat CD, and our comparison in the same in vitro settings of different pharmacological induction agents. Our study also had some weaknesses in that we analyzed the effects of pharmacological induction agents on myometrial contractility, whereas the physiology of labor induction indicates that cervical ripening and uterine contractions often occur concurrently after PG administration. Similarly, our ex vivo model may not reflect the complexity of molecular interactions occurring in vivo; and the small sample size can be a limitation of our survey. In summary, our study contributes to explain how direct myometrial effects can only partially explain the mechanism of action of pharmacological induction agents. Further studies are needed to evaluate the interaction between the uterine cervix and myometrium during labor induction and how it affects myometrial contractions. A better understanding of the mechanisms of action of labor induction would allow clinicians to perform safer and more effective inductions of labor.

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Figure1. Baseline contractility

Kruskal-Wallis One Way Analysis of Variance on Ranks $p = 0.3$. Oxy: oxytocin.

Figure 2. Effect of cumulative concentrations of oxytocin, PGE1 and PGE2 on uterine contractility

Kruskal-Wallis One Way Analysis of Variance on Ranks followed by Dunn's post hoc test * $p < 0.05$, oxytocin vs PGE1, PGE2 & CTR. Data are reported as median [IQR]. Oxy: oxytocin

Figure 3. Effect of cumulative concentrations of PGE1 and PGE2 on uterine contractility
 Kruskal-Wallis One Way Analysis of Variance on Ranks followed by Dunn's post hoc test *
 $p < 0.05$, PGE1 vs CTR. Data are reported as median [IQR]. Oxy: oxytocin.

Table 1

Characteristics of study participants

Age (years)	26.9 $\pm$ 4.5
Gravidity	3 [2-3]
Parity	2 [1-2]
Number of prior CD	1 [1-1]
Gestational age (weeks)	39.3 $\pm$ 0.3
Race/Ethnicity	
Caucasian	1 (7.7%)
African American	2 (15.4%)
Hispanic	10 (76.9%)

CD = cesarean delivery; data are reported as mean $\pm$ SD, median [IQR], or n (%)