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ARTICLE

Maternal parity and functional contractility of human myometrium in vitro in the third trimester of pregnancy

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Abstract

Objective It is well established that the duration of the first and second stages of labor are shorter in parous women than in their nulliparous counterparts, a phenomenon not well understood. The aim was to examine the effect of maternal parity on contractile parameters of human myometrium.

Design Myometrial strips were excised from $n = 74$ women at cesarean delivery and recordings of contractile activity analyzed and compared across three clinical groups: 1. No previous delivery (P0); 2. One previous delivery (P1); 3. Greater than one previous delivery (P>1).

Results There was a trend towards greater mean contractile force in the P>1 group than the P1 and P0 groups ($P = 0.412$). Frequency of contractions was less in the P1 group than in the P0 and P>1 groups($P = 0.027$). No differences were observed in relation to all other parameters.

Conclusion Excluding frequency, no intrinsic differences were observed in the functional parameters of human uterine contractions in relation to parity.

Introduction

It is well established that the contractile activity of the human uterus in labor, in a parous woman, is different to that of the nulliparous woman. The duration of the first and second stages of labor are shorter in the parous woman in comparison to her nulliparous counterpart [1]. Dysfunctional uterine contractility, often resulting in failure to progress in labor, may occur in up to 30% of nulliparous women [2, 3], and in recent years has contributed to increased medical intervention and cesarean delivery in this group [3, 4]. While the reasons for this are potentially many and complex, and may be of maternal or fetal origin, the biological processes that underlie this phenomenon are not known. In particular, the physiological links between efficiency of uterine contractions, and the allied processes of cervical dilatation and descent of the fetal head, are poorly understood [5]. This is due, in part, to the fact that the methodology available for detailed clinical assessment of uterine contractions in human labor is limited from a practical viewpoint and exhibits many pitfalls in the ascertainment of reliable quantitative data [6]. At a time when our understanding of the molecular mechanisms underlying parturition has improved considerably [7], it remains the case that our knowledge regarding the functional parameters of human uterine contractions is quite limited.

The use of in vitro pharmacological studies represents another approach for assessment of functional aspects of human myometrial contractions in isolated tissue preparations and has become more widespread in recent years [8]. Technological advances in the design of data acquisition systems, and their associated software, has facilitated researchers in examining many different parameters of uterine contractions over varying periods of time, and our group have previously reported on these in varying clinical situations [8–10]. To our knowledge, there are no data reported regarding the effects of parity on the subtle properties of human uterine contractions in pregnancy, either from in vitro, in vivo, or clinical experiments. The purpose of this study was to examine a range of contractile parameters of human myometrium, obtained during pregnancy,

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in vitro, in relation to maternal parity. The findings from this study have been presented at Society for Maternal Fetal Medicine (SMFM) Pregnancy Meeting, Dallas TX, USA February 2018 [11].

Material and methods

Tissue sample collection

Myometrial biopsies were obtained from planned cesarean deliveries performed in the third trimester of pregnancy in the Department of Obstetrics and Gynecology, Galway University Hospital, Galway, Ireland. Institutional review board approval was obtained from the Research Ethics Committee at Galway University Hospital (Ethics Reference Number C.A 1758—Collection of Reproductive Tissue Samples at Time of Delivery). All of the samples were obtained from the upper lip of the incision in the lower uterine segment as described previously [9, 12, 13]. All samples were obtained from donors after receiving written informed consent. All women recruited had cesarean section procedures performed before the onset of labor. All women in the study were scheduled for a planned cesarean delivery, i.e. at a time suited to both the woman and the medical staff. None of the women in the study were clinically in labor or having spontaneous contractions. Exclusion criteria included maternal age < 18 years, maternal blood-borne infections, administration of exogenous oxytocin or prostaglandin agents, and if there was a lack of patient understanding or capacity to consent. For this study women who had a history of either a vaginal delivery in previous pregnancy, or a past history of labor in a previous pregnancy, were excluded from analysis, as were women with multiple pregnancy and those <36 weeks gestation (Fig. 1). Labor was defined as cervical dilatation of ≥4 cm. This was done in an effort to assess the effect of parity alone, i.e. apart from the effects of having had a previous labor or vaginal delivery, on myometrial contractility. Separate studies, which included use of some of the biopsies used in the current work, have already been reported in different contexts [9, 10].

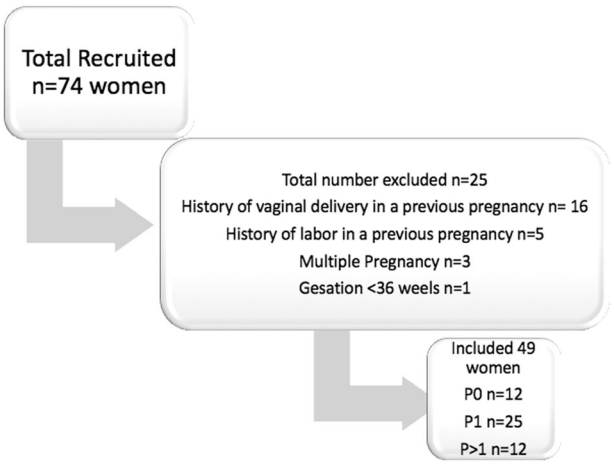

Fig. 1 Exclusion criteria

Following collection of the samples in the operating theater, they were placed in physiological salt solution (PSS) at 4 °C. The PSS contained the following ingredients: 4.7 mmol/L potassium chloride (KCl), 118 mmol/L sodium chloride, 1.2 mmol/L magnesium sulfate, 1.2 mmol/L calcium chloride, 1.2 mmol/L potassium sulfate, 25 mmol/L sodium bicarbonate, and 11 mmol/L glucose (Sigma-Aldrich, Dublin, Ireland). Specimens were transported to the laboratory within 2 h of collection, transferred to fresh PSS at room temperature, and used for experiments within 15 h [9].

Tissue bath experiments

Myometrial tissue was dissected and prepared for tissue bath analysis, as previously described [8, 9, 14]. Decidua and serosa were dissected away, and tissue samples were dissected into eight uniform strips of 2 × 2 × 10 mm. Only biopsies from which eight strips were obtained were included in the study. Once prepared the myometrial strips were mounted in tissue baths containing 20 mL of PSS, pH 7.4 at 37.4 °C as previously described [9] and were gassed continuously with a mixture of 95% oxygen/5% carbon dioxide. The strips were then stretched to a resting tension of 20 mN and allowed 30 min equilibration time. Fresh PSS was then introduced, and the tension readjusted to 20 mN and equilibrated for a further 15 min [10]. A period of spontaneous activity, without any further intervention, was then recorded for 130 min.

Contractile activity measurements and data analysis

Contractile activity was recorded using PowerLab/8SP recording unit writing to Chart v4.0 software (AD instruments, Oxford, UK). The resulting digital files were then analyzed using LabChart v7.37 (AD Instruments). Data were extracted using custom macros and the results exported to Microsoft Excel for final analysis [10].

The following parameters of contractile performance were measured: the maximum amplitude of contractions (MAMP); the mean contractile force above baseline (MCF) for spontaneous contractions over the 130-min period; the time to first contraction; the time to achievement of MAMP; the maximum rate of rise of contractions; the maximum rate of relaxation of contractions. Individual contractions were defined as simple, biphasic, or multiphasic, as previously described [9, 10]. The percentage of total contractions that

Table 1 Demographic details of participants

	Overall group demographics ($n = 49$)	P0 ($n = 12$)	P1 ($n = 25$)	P>1 ($n = 12$)	Statistical significance
Mean age (years)	35.5	36.9*†	35.1*	34.7†	*$P < 0.01$ †$P < 0.01$
Mean BMI (kg/m^2)	26.2	25.6	26.6	25.96	ns
Parity					
Median	1	0	1	2	ns
Range	(0–7)			(2–7)	
Gestation at delivery					
Median range	38 + 6	39	39	38 + 4	ns
(weeks+days)	(36 + 6–41 + 1)	(36 + 6–40 + 6)	(38–41 + 1)	(37 + 4–39 + 3)	

P0 = Women with no previous delivery (Para 0). P1 = Women with one previous delivery (Para 1). P>1 = Women with more than one previous delivery (Para >1)

*Denotes comparison between P0 and P1 groups; †Denotes comparison between P0 and P>1 groups; ns = not significant

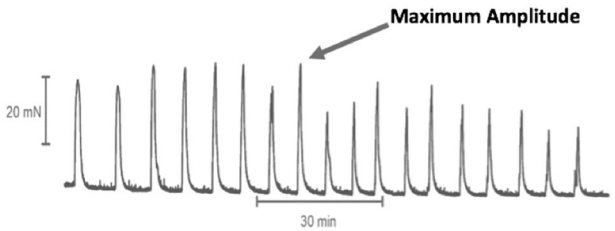

Fig. 2 Representative image of contractile activity of myometrial sample displaying point of measurement of maximum amplitude

were biphasic or multiphasic were described for each strip. The frequency of the contractions was also examined. For the determination of frequency, the number of contractions over the entire 130-min time period was determined using labchart's peak analysis module. The peak analysis type was set to "general—unstimulated" with a minimum peak height of 2 mN. Baseline was determined from the minimum value between peaks with TStart as the first point 5% of the height away from the baseline and TEnd as the last point 0% of the height away from the baseline.

For each parameter, values derived from every individual strip were analyzed and compared between three clinical groups as follow: 1. Women of zero parity, i.e. with no previous delivery (P0); 2. Women with one previous delivery (P1); 3. Women with more than one previous delivery (P>1). For descriptive statistics and analysis the arithmetic mean for each contractile parameter was determined for all eight strips from each donor. Demographic data were reported as mean or median values. Statistical analysis across the groups was performed using a one-way ANOVA (IBM SPSS Version 24). If the ANOVA indicated a significant difference between groups it was followed by post hoc analysis using Tukey's HSD test to determine which groups were different from each other, and a P value of <0.05 was accepted as statistical significance.

Results

Myometrial biopsies were taken from $n = 74$ women. The exclusion criteria applied for previous vaginal delivery ($n = 16$), history of previous labor ($n = 5$), multiple pregnancy ($n = 3$), and gestation <36 weeks ($n = 1$) resulted in data from $n = 49$ women for inclusion. The demographic features of women recruited are outlined in Table 1. The mean maternal age was 35.5 years (range 23–44 years). The mean maternal body mass index was 26.2. The median parity of the women was 1 (range 0–7), 12 women were nulliparous, 25 women had one previous delivery, and 12 women had greater than one previous delivery. The P>1 group ($n = 12$) had a range of 2–7 previous cesarean deliveries, with a median of 2. The average gestation at delivery was 38 + 6 weeks gestation (range 36 + 6–41 + 1 weeks gestation). The maternal demographic features subdivided by clinical group are provided in Table 1. The average age for the P0 group (36.9 years), was significantly greater than that of the P1 group (35.1 years; $P < 0.01$), and also greater than the average age of the P>1 group (34.7 years; $P < 0.01$). There was no difference observed in any of the other demographic features between the groups.

The reasons for cesarean delivery were as follows: previous cesarean delivery $n = 34$; complications of pregnancy/maternal medical issues (pre-eclampsia, hypertension, and cholestasis) $n = 7$; breech presentation $n = 4$; maternal choice $n = 2$; previous myomectomy $n = 1$; and previous pelvic fracture $n = 1$. Eight uniform strips were

Table 2 Contractile parameters

	P0 ($N = 12$)	P1 ($N = 25$)	P>1 ($N = 12$)	Statistical significance
MAMP (mN)	35.6 ± 10.3	31.1 ± 6.3	41.6 ± 12.0	ns
Time to MAMP (min)	51 ± 14.7	49.5 ± 7.4	54.7 ± 15.8	ns
Time to first contraction (min)	10.4 ± 3.0	14.1 ± 2.1	10.5 ± 13.0	ns
MCF (mN)	3.5 ± 1.0	3.9 ± 0.6	4.8 ± 1.4	ns
Rate of rise (mN/s)	2.5 ± 0.7	2.9 ± 0.3	3.6 ± 1.0	ns
Rate of relaxation (mN/s)	−2.2 ± −0.6	−1.8 ± 0.8	−2.9 ± −0.8	ns
% Biphasic	19.3 ± 5.6	17 ± 2.8	23 ± 6.6	ns
%Multiphasic	10 ± 2.9	8.4 ± 2.2	10 ± 2.9	ns
Frequency (Hz)	8.3 ± 2.4	5.2 ± 0.7	8.3 ± 2.4	*$P < 0.05$ ■$P < 0.05$

The values given are arithmetic means ± standard errors of the means of parameters obtained from each donor

P0 = women with no previous delivery (Para 0). P1 = women with one previous delivery (Para 1). P>1 = women with more than one previous delivery (Para >1)

MAMP the maximum amplitude of contractions, *MCF* the mean contractile force above the baseline, *ns* not significant

*Denotes comparison between P0 and P1 groups; ■ Denotes comparison made between P1 and P>1 groups

obtained from each of the 49 women, giving a total of 392 strips for analysis of spontaneous contractile activity. The patterns of spontaneous contractile activity were recorded and analyzed for each individual strip. Figure 2 demonstrates a representative recording of raw data obtained from a single myometrial strip. The arithmetic means ± standard errors of the means (sem) of all contractile parameters from each patient donor, from each of the three clinical groups (P0, P1, and P>1), are displayed in Table 2 for comparison.

There were no significant differences observed in the following contractile parameters in relation to maternal parity; MAMP, MCF, time to first contraction, rate of rise of contractions and frequency. There was a trend towards greater MCF with increasing parity, but this was not significant ($P = 0.412$). The MAMP achieved was similar in the P>1 group, in comparison to both other groups (Table 2). No difference was observed in the proportion of biphasic or multiphasic contractions between the three different groups. Finally, the frequency of contractions observed was lower in the P1 group than in both other groups (Table 2).

Conclusion

These findings indicate that apart from frequency of contractions there are no intrinsic differences in the functional myometrial contractility of human uterine tissue obtained in the third trimester of pregnancy in relation to maternal parity. There was a trend observed towards increased contractile force with parity, but this was not significant. No difference was observed in the occurrence of biphasic or multiphasic contractions. The strengths of this study include the large numbers of experiments performed, the number of contractile parameters examined, and the focus on the effects of parity separately from previous vaginal delivery or labor. In addition, there are no published reports on this topic to our knowledge.

One of the central conclusions from this study is that parity is not associated with a greater mean force or amplitude of uterine contractions throughout the period of time analyzed. The authors have been unable to identify any previous report, using in vitro or in vivo methodology, from human or other animal model type, which has specifically addressed this issue. Consequently, it is not possible to compare our findings with those previously reported. These results contribute to the biological understanding of functional contractility in human labor but do not explain the shorter duration of labor [15], and the lower incidence of dysfunctional labor [16, 17], associated with the parous woman.

In this study, we excluded myometrial tissue obtained from women who had previously undergone labor or vaginal delivery, so the findings outlined are mainly associated with maternal parity. In addition, the demographic features of the women recruited for biopsy donation were similar in all respects with the exception of maternal age. The mean age of the nulliparous women was 36.9 years, in comparison to 35.1 and 34.7 years, in the P1 and P>1 groups, respectively. We appreciate that there is controversy about the potential effects of maternal age on uterine contractility in labor, and particularly from a clinical perspective. However, we have previously reported that analysis of a wide range of functional contractile parameters, in human pregnant myometrium in vitro, revealed no significant

difference with maternal age, in a cohort of 32 women aged between 28 and 52 years [9]. This is consistent with a study by Arrowsmith et al., who observed that contractile force was maintained in pregnant women up to around 40 years of age [18]. We are therefore of the view that the age difference between groups in this study is unlikely to have contributed to the findings noted. Finally, all women recruited were between 36 + 6 and 41 + 1 weeks of gestation, representing the latter half of the third trimester.

The authors acknowledge that the indications for cesarean delivery varied somewhat among one-third of the women recruited, while in the remaining two-thirds the procedure was done because of previous cesarean delivery. It has been reported that myometrium obtained from women whose previous cesarean delivery was done for fetal compromise, or acidosis, contracted with more force in comparison to tissue obtained from women for whom delay in labor was the reason for cesarean section [19]. It was not possible in this study to examine the various indications for cesarean delivery, in the three separate groups, in a meaningful way, in order to evaluate if reasons other than parity exerted an effect. Finally, and perhaps most interestingly, it remains unknown whether or not labor would have exerted an effect on the measurements obtained. Finally, there was an increased frequency of contractions noted in the PO and P>1 groups in comparison to the PI group. It has been suggested from some clinical studies that frequency of contractions was greater in primigravid women in comparison to multiparous women, both in induced and in spontaneous labor [20], We are unaware of any reports pertaining to frequency and increasing parity and are unable to explain fully the findings observed here. These is a topic for further study, and it is difficult to extrapolate sound clinical conclusions from these findings observed in vitro.

In conclusion, the results of this study demonstrate that many basic parameters of human myometrial contractility are not altered with increasing maternal parity. These findings contribute to a biological understanding of human uterine contractions but do not explain the shorter duration of the stages of labor that occur in parous women and raised further questions regarding the labor process.

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Author contributions JJM and DJC conceived and designed the study. All authors were involved in data analysis, writing, and revising the manuscript and all authors have approved the final manuscript submitted. GAR, as the corresponding author, confirms that she has full access to the study data and full permission of all authors to submit for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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