**Maternal phenotype: How does age, obesity and diabetes affect myometrial function?**

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**Abstract**

The prevalence of obesity and diabetes has increased rapidly in the general population over the last few decades, meaning that a significant number of women of reproductive age are now classified as obese and/or suffering from diabetes. More and more women are also delaying childbearing until older ages. This shift in maternal phenotype is accompanied by an increase in adverse pregnancy and labour outcomes. This review will summarise our current understanding of how maternal age, obesity and diabetes affect myometrial contractility and how these changes impact clinical outcomes.

**Key words:** Maternal age, Obesity, Diabetes, Myometrium, Contractility

**1.0 Introduction**

Myometrial smooth muscle is myogenically active and the process of excitation-contraction coupling in the uterus has been comprehensively reviewed elsewhere [1]. Maternal phenotype (advanced age, obesity, diabetes) can impinge upon the process of myometrial contraction, increasing the risk of dysfunctional labour and adverse pregnancy outcomes. In this review we will look at the increased risks associated with the maternal phenotypes of advanced maternal age, obesity and diabetes and examine what evidence exists for changes to myometrial contractility being the root cause of the dysfunctional labours.

**2.0 Advanced maternal age**

More women in the UK are delaying childbearing until older ages, due to a variety of factors, such as increased female participation in education and the work force, widespread access to effective contraception and improved assisted reproduction techniques [2]. Similarly, in the US, there were 9 times more first births to women aged 35 and over in 2012 compared to 4 decades previously [3] and mean age of first birth has increased from 24.9 to 26.3 from 2000-2014, with fewer babies born to the under 20s and more to over 35s [4].

Embarking on first time motherhood at ≥35 years of age comes with increased occurrence of co-morbidities (gestational diabetes, obesity, hypertension, preeclampsia) and worse infant and maternal perinatal outcomes (stillbirth, small for gestational age babies, preterm birth, low APGAR scores, maternal death) [5-8]. The majority of clinical studies demonstrate duration of labour is extended in the older mother [6, 9-12] and an increase in the rate of both elective caesarean sections (CS) and emergency interpartum CS as maternal age increases, as well as increased induction of labour, risk of CS after induction and increased risk of operative vaginal delivery [5, 6, 8-10, 13-16]. One recent study however did not observe a difference in CS rate or a prolongation of labour after spontaneous labour in older women [17]. There has been debate therefore as to whether or not the process of parturition is actually altered or less efficient in the older mother (i.e. is there an underlying biological cause?), as opposed to the higher rate of CS reflecting a physician or maternal choice. There are a limited number of in-vitro studies attempting to address this question in human and animal myometrial tissue strips.

Multiparous mice at the extreme end of reproductive viability (11-12 months) exhibit longer gestations than younger multiparous mice (3-7 months), possibly because of a delayed reduction in progesterone levels [18]. Another study demonstrated that 8 month old nulliparous mice (an age more relevant to older pregnant women) had prolonged gestation and labour, and reduced litter size compared to 3 month old mice [19]. Strips of myometrial tissue produced spontaneous contractions that were more frequent but of lower duration in aged late-pregnant mice, and the response to stimulation with oxytocin (OT) was reduced. OT receptor expression and connexin 43 expression were found to be reduced and could be potential causes of labour dysfunction [19]. In a rat model, greater spontaneous contractility of myometrial strips was apparent in young animals (8w) compared to 24 week olds, although the expression of contractile-associated proteins (including connexion 43) was unaltered [20].

A similarly small number of studies have been undertaken in isolated human myometrium (Table 1 for Summary). Smith et al. (2008) [16] showed that spontaneous contractile activity in-vitro decreased with increasing age in non-labouring term pregnant human myometrium. Interestingly there were more multiphasic contractions in myometrium from older mothers, which has previously been associated with prolonged labour and increased risk of intrapartum CS [21]. More recently, Arrowsmith et al. (2012) [22] demonstrated a decreased force of contraction with increasing age (spontaneous and K+-stimulated) in non-pregnant human uterus (age range 25-72 years). A similar trend was observed in pregnant uterus but did not reach significance. It may be that pregnancy hormones causing hyperplasia and hypertrophy of myometrium can restore age-related deficits. There was a trend towards a reduced response to OT, but this also did not reach significance [22]. Similarly, Crankshaw et al. (2015) [23] found no correlation between maternal age and myometrial contractility in-vitro (spontaneous, K+ or OT-stimulated) in term pregnant women and no evidence for an increased rate of multiphasic contractions.

It has been suggested that the reduction in oestrogen levels accompanying the normal aging process could result in myometrial atrophy and reduced spontaneous contractions [22]. This may be the case in post-menopausal myometrium, however smooth muscle cell and extracellular matrix content in term pregnant human myometrium at least is unaltered [24]. Any deficits in function therefore are likely to be related to smooth muscle cell signalling pathways/ion channel function/membrane potential/electrical coupling between cells (gap junctions). One study has shown increased KATP channel expression in myometrium from older mothers [25]. Normally in late pregnancy, KATP channels are downregulated, allowing the increase in excitability required for labour onset [26]. Failure to downregulate these channels could dampen contractility and produce a prolonged or dysfunctional labour.

Work in this area is fairly limited to date and we do not yet have a clear answer to the question of whether advanced maternal age directly alters myometrial contractility. Further studies are therefore required to resolve this conundrum and to delve more deeply into the relevant mechanisms.

An intriguing recent hypothesis is that age at menarche is an important factor in pregnancy outcome [27]. Early menarche exposes the uterus to prolonged cyclical oestrogen/progesterone stimulation, impairing myometrial function and predisposing to operative delivery. Later menarche appears to reduce the risk of operative first birth by shortening the menarche to first birth interval [27, 28].

**3.0 Obesity**

Worldwide obesity rates have more than doubled since 1980, with 39% of adults being overweight and 13% obese [29]. Maternal obesity in the UK also more than doubled from 7.6% to 15.6% from 1989 to 2007 [30] and recent data from the USA found the incidence of obesity in the pregnant population to be even higher (27.8%) [31, 32].

Obese pregnant women are at an increased risk of many maternal and perinatal complications, and the risks are amplified with increasing degrees of maternal obesity [33, 34]. Maternal obesity (BMI≥30) is a well-recognised risk factor for diabetes, preeclampsia, still birth, preterm birth, congenital abnormalities and macrosomia [6, 35-39]. It is also associated with complications during labour and delivery (longer duration of the first stage of labour, inductions, CS and instrument-assisted births) [6, 39-44]. The finding of a longer gestation period and higher risk of post-dates delivery in obese women [45, 46] will also contribute to the greater need for induction of labour and CS, as well as increased risk of perinatal morbidity and mortality.

Dysfunctional labour/ineffective uterine contractility, leading to slow progress of labour, is the most common cause of unplanned CS in obese women [42, 44, 47]. This suggests that myometrial contractility may be impaired in obese women. Obese women delivering vaginally experience greater blood loss than normal weight women [44], which is also consistent with poor myometrial contractility. Indeed it has been demonstrated in-vitro that force and frequency of spontaneous human myometrial contractions are reduced as maternal BMI increases, and this results from reduced Ca2+ transients [44]. Other studies however did not find a correlation between spontaneous or OT-mediated contractions and maternal BMI in human myometrium [48, 49]. More recently, Crankshaw et al. (2017) observed a positive correlation between BMI and contraction amplitude and force in term pregnant human myometrium, and no alteration in the proportion of strips with multiphasic contractions [50]. They did however note an increased time to onset of contractions and time to reach maximal amplitude of contraction. These contradicting results may be due to experimental differences or the inevitable difficulty of controlling for confounding factors around obesity.

The molecular mechanisms by which obesity leads to prolonged or difficult labours have been probed to some extent over the past 10 to 15 years, but much remains to be clarified. Some of these mechanisms are reviewed below.

**3.1 Dislipidemia**

Dislipidemia is a feature of obesity, including in obese pregnant women [51, 52]. Cholesterol is a vital component of caveolae, and changes to the cholesterol environment can alter signalling of the receptors and channels located within these lipid rafts. Caveolae are a feature of uterine smooth muscle cells and reducing cholesterol content (using the cholesterol-sequestering agent, methyl-β-cyclodextrin (MCD)) significantly increases the contractility of human myometrial muscle strips in-vitro and correspondingly, increasing cholesterol content decreases contractility [53]. This altered contractility is related to changes in intracellular Ca2+ signalling, upon which uterine contractility is intimately dependent. In particular, in isolated myometrial myocytes, MCD increased contractility by decreasing outward current through the large conductance Ca2+-activated K+ (BK) channels, leading to depolarisation of the membrane potential and firing of action potentials [54]. An older study found decreased membrane lipid fluidity in cases of poor myometrial contraction during labour, which was associated with higher total cholesterol and lower phospholipid content in myometrial membranes [55], although another study demonstrated that early pregnancy plasma cholesterol levels were not related to risk of CS [56]. It may be that cholesterol levels at mid or late term of pregnancy will be more relevant to successful labour outcomes.

Similar cholesterol-mediated inhibition of myometrial contractility is seen in rats and guinea-pigs [57, 58], and sequestration of membrane cholesterol (with MCD) causes increased contractility [58]. Application of a high fat, high cholesterol diet in rodents alters lipid profiles (increased plasma cholesterol and triglycerides), decreases expression of caveolae and gap junction proteins, results in poorly coordinated myometrial contractions and attenuates the OT response due to loss of OT receptors [59-61]. A transgenic mouse model characterised by cholesterol ester accumulation in the myometrium (nuclear oxysterol receptor knockout mouse) exhibits a reduced OT response and abnormal labours [62].

**3.2 Inflammation**

Parturition itself is sometimes described as an inflammatory process. Physiological labour is associated with a massive influx of inflammatory cells into the myometrium, an upregulation of pro-inflammatory cytokines and iCAM expression [63]. Obesity is also characterised as a state of low-grade chronic inflammation and multiple inflammatory mediators are further elevated in obese mothers compared to their lean counterparts [51, 64-66]. TNFsecreted by adipocytes, can stimulate the generation of reactive oxygen species (ROS), as can mitochondrial metabolism of the excessive free fatty acids that are present in obese tissues [67]. The resulting oxidative stress is implicated in the development of pathologies such as metabolic syndrome and atherosclerosis.

**3.2.1 Cytokines and reactive oxygen species**

There is evidence that pro-inflammatory cytokines have a direct effect on myometrial contractility: for example, IL-1 induces basal and store-operated Ca2+ entry in isolated human myometrial cells, increasing contractility [68]. IL-1 also increases phosphodiesterase activity, stimulating myometrial contraction via the breakdown of cAMP (which plays a role in maintaining quiescence) [69]. Reactive oxygen species (superoxide, H2O2) have also been demonstrated to have a direct effect on human myometrium. Superoxide increases human myometrial contraction in isolated muscle strips [70] and increases intracellular Ca2+ in isolated human myometrial cells, which would be expected to increase contractility in an intact tissue [71]. One study however showed superoxide and H2O2 to inhibit the OT-stimulated contractions of human myometrium [72].

While it is clear that an increased state of inflammation occurs in obese pregnant mothers and that elevated cytokines/ROS have the potential to directly alter myometrial contractility, there are no studies on human myometrium from obese and normal weight mothers to directly demonstrate this.

**3.3 Adipokines**

An alternative mechanism by which obesity may affect uterine contractility, is release of adipokines by adipose tissue. In obesity, adipocytes become dysfunctional, producing more pro-inflammatory, atherogenic adipokines and less anti-inflammatory insulin-sensitising adipokines. This unbalanced production of adipokines plays a key role in development of obesity-related pathophysiology [73, 74]. A number of adipokines affect myometrial contractility, for example, visfatin, leptin, apelin and ghrelin. Visfatin and leptin inhibit human and rat myometrial contraction in-vitro [75, 76]. To date, clinical studies are contradictory, with higher cord blood leptin levels being associated with prolonged labour [77], or maternal plasma leptin levels not being associated with the duration of the active phase of labour [78]. They suggest that the relatively low % of obese women in their study may explain the lack of significant association. The effect of ghrelin and apelin on myometrial contraction is less clear. Both were shown to have an inhibitory effect on human and/or rat myometrial contractility [79-81], but another research group found both adipokines to have a stimulatory action on rat myometrium [82, 83]. Clearly, altered adipokine levels have the potential to play a significant role in parturition, but further clinical and pre-clinical studies are required to tease out their role.

**3.4 Placental corticotropin-releasing hormone**

Maternal plasma concentrations of corticotropin-releasing hormone (pCRH) rise exponentially as pregnancy progresses towards term (produced by the placenta). The changing concentrations of pCRH have been described as a ‘placental clock’, determining the length of gestation and the timing of the onset of parturition, with high pCRH levels being associated with preterm birth and low levels associated with postdates birth [84]. Levels of pCRH are significantly decreased in obese pregnant women compared to their lean counterparts [85, 86], which may account for the longer gestation period experienced by obese mothers. Studies on isolated human myometrium have demonstrated that CRH can potentiate the contractile activity of OT [87] and PGF2[88]. Additionally, KATP channel expression in human myometrial cells is regulated by CRH, with a low concentration of CRH upregulating KATP expression and a high concentration downregulating KATP expression [89]. Therefore, obesity-related lowering of CRH levels will help maintain high KATP expression and uterine quiescence. pCRH exerts its effects on foetal as well as maternal tissues and can result in increased prostaglandin and estriol expression [90], which will also affect myometrial activation and sensitivity. The lower levels of pCRH exhibited by obese pregnant women may therefore impact on myometrial contractility through these multiple different pathways.

**3.5 Contractility-associated proteins**

The effect of obesity on human myometrial OT receptor expression remains unclear, with some studies noting that OT receptor mRNA is upregulated with increasing maternal BMI [91] and others identifying no link between maternal BMI and OT receptor gene and protein expression [92], although in this last study 33% of subjects were labouring and the rest non-labouring, which may complicate interpretation of the results. As mentioned earlier, rodent models of obesity appear to demonstrate loss of OT receptors and thus an attenuated OT response. Whether obesity affects gap junctions in human myometrium also remains unclear. On the one hand, we see prolonged labour associated with lower expression of connexin 43 in a mixed weight pregnant population [93], however in another study, connexin 43 expression was unaltered in term pregnant women undergoing elective CS [91].

Other potential mechanisms whereby obesity affects myometrial contractility have been suggested. Human Ether-à-go-go (h-ERG) channels play a role in uterine quiescence. At term, beta-inhibitory protein is upregulated, reducing h-ERG activity and increasing duration of action potentials and contractions. An interesting study by Parkington et al. (2014) reported that obese women have low expression of beta-inhibitory protein which may lead to weaker contractions and poorer labour outcomes [94]. P160 ROCK-1 expression, which plays a role in Ca2+ sensitisation, is decreased in obese myometrium in late gestation, which could contribute to an inhibitory effect on contractility at labour [95].

**3.6 Smooth muscle content**

An obesity-related decrease in myometrial contractility could also be caused by decreased myocyte number, which was found to be the case in one study of term pregnant human uterus [96], though another found smooth muscle cell content and extracellular matrix content in term pregnant human myometrium to be unaltered [24]. (See Table 1 for Summary).

**3.7 Mitochondrial dysfunction**

Obesity has been demonstrated to bring about mitochondrial dysfunction in many different animal and human tissues (see [97] for review).

Maternal obesity causes an impairment of mitochondrial function in the placenta [98, 99], that may compromise placental function and a play a role in adverse fetal and pregnancy outcomes. However the only study to examine mitochondrial function in human myometrial smooth muscle reported no change in obese pregnant women [96]. This was also confirmed in a high-fat diet, pregnant rat model [100].

**3.8 Artery dysfunction**

Further evidence of the detrimental role of maternal obesity is observed in the altered function of small human myometrial arteries isolated from obese mothers undergoing elective CS [101, 102]. Deficits in endothelial cell calcium signalling and the eNOS system result in failure of vessels from obese mothers to relax normally [101]. Myometrial vessels are repeatedly compressed during labour contractions. The removal of metabolites of oxidative stress and intracellular acidification from one contraction to the next, requires occluded vessels to dilate fully. Thus impaired relaxation and an inability to fully recover following compression during contractions, might also contribute to poor labour outcomes in obese women.

**4.0 Diabetes**

8.4% of adults globally are living with diabetes and 16.2% of live births are affected by hyperglycaemia in pregnancy [103]. The prevalence of births complicated by pre-existing diabetes rose by 50% from 1996-2004, driven by a sharp increase in type II diabetes [104]. Rates of gestational diabetes vary considerably depending on ethnicity (from 6.1% in Europe to 15.2% in North Africa and the Middle East [105].

Women with diabetes have significantly increased risk of pre-eclampsia, still birth, fetal congenital abnormality, perinatal mortality, large for gestational age babies, preterm delivery, shoulder dystocia, emergency CS and post-partum haemorrhage, compared to the general maternity population [106-112]. The Confidential Enquiry into Maternal and Child Health (CEMACH) report on ‘Diabetes in Pregnancy’ confirms these findings and reports a caesarean section rate of 67% for diabetic women [113]. More than 50% of emergency CS in diabetic mothers are due to prolonged labours and failed induction of labour [114] and post-partum haemorrhage occurs 6 times more often in diabetic mothers [110], which again could indicate a dysfunction of the myometrial smooth muscle.

The only study to look in detail at the contractile response of human diabetic myometrium, shows that spontaneous contractions are smaller and of shorter duration than in normal controls [115]. Oxytocin stimulates contractions but the impairment remains, as OT-stimulated contractions are still smaller in diabetic samples. The response to high K+ is reduced, due to reduced L-type Ca2+ channel expression and activity. So once again, changes in Ca2+-signalling are implicated as the mechanism behind myometrial dysfunction. The only other study to examine contractility of human diabetic myometrium found an increased response to endothelin-1 in diabetic muscle strips [116]. They noted that stability of spontaneous contractions was poorer in diabetic samples, that is, amplitude of contractions decreased more rapidly over time. Various rat and mouse models of diabetes have been developed [117]. Non-pregnant diabetic rats exhibit reduced OT-mediated stimulation of myometrial contractility [118] and spontaneous contractions that fade more rapidly over time [119]. Pregnant diabetic rats also exhibit spontaneous myometrial contractions that fade more rapidly than in controls and alterations to OT signalling [120, 121]. Consistently, we see loss of myometrial muscle mass and myofilament number in diabetic animal models [118, 122, 123]. In pregnant human myometrium, Al-Qahtani et al. (2012) found a small but significant decrease in myometrial muscle mass that may contribute to reduced contractility [115], but another study found no morphological changes [124], the differences perhaps reflecting the different diabetes diagnoses in the pregnant populations examined (see Table 1 for Summary). No differences in mitochondrial function, content or morphology were detected in myometrial samples from women with diabetes [124].

The global increase in diabetes appears to be fuelled by the increase in obesity. In fact, obesity is believed to account for 80-85% of the risk of developing type II diabetes [125, 126]. However, diabetes is also an independent risk factor for CS and other pregnancy-related problems [127]. It is also becoming clear that there is no obvious threshold effect, that is, there is a continuously increasing risk of clinically important perinatal problems with increasing glucose levels [128, 129]. In addition, we are beginning to understand that risks that are increased with obesity and diabetes alone, are even further increased with both together [127].

**4.1 Artery dysfunction**

It is well known that one of the major side effects of diabetes is vascular damage [130] and this extends to human myometrial and uterine arteries, which exhibit a deficit in endothelial-dependent relaxation [131, 132] and hyperreactivity of vascular smooth muscle [132]. Such vascular deficits may well play a role in myometrial dysfunction and poorer pregnancy outcomes experienced by diabetic women.

**5.0 Conclusions**

Clinical data published in the last 2 years strongly points to pregnancies complicated by advanced maternal age, obesity and diabetes being more risky and having worse outcomes. With these maternal phenotypes, risk of dysfunctional labour and caesarian section is increased and understanding the mechanisms by which this occurs will help us provide better perinatal care and hopefully improve outcomes. Studies on isolated human and animal myometrium point to clear deficits in myometrial contractility, caused by a variety of signalling changes, but there are few recent studies and many gaps in our knowledge. The effects of each phenotype are likely to be multifactorial, there is a close relationship or overlap between phenotypes (e.g. older mothers are more likely to have higher BMI/diabetes) and their prevalence is forecast to grow strongly in the coming decades. Encouragement of healthy lifestyle choices to reduce pre-pregnancy obesity and rigorous control of maternal glucose levels will help improve outcomes, but given the impact of these phenotypes on successful parturition, it will become ever more vital for us to understand the cellular mechanisms involved, with the aim of improving perinatal care and pregnancy outcomes.

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**Declarations of Interest**

None

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**Annotated References**

The following references have been selected as papers of special interest (\*) or outstanding interest (\*\*).

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\*\*[105] McIntyre, H.D., et al., *Gestational diabetes mellitus.* Nat Rev Dis Primers, 2019. **5**(1): p. 47.

Exceptional review of Gestational Diabetes, including risk factors, pathophysiology, maternal and fetal consequences, management/interventions and areas for future research.

\*[107] Mackin, S.T., et al., *Diabetes and pregnancy: national trends over a 15 year period.* Diabetologia, 2018. **61**(5): p. 1081-1088.

Examines trends and perinatal outcomes in pregnancies complicated by diabetes over a 15 year period, demonstrating the % rise in diabetes, and the increased risk of perinatal outcomes for Type I and Type II diabetics.

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**Table 1:** Summary of experimental evidence for the effect of maternal phenotype (advanced maternal age, obesity and diabetes) on human myometrial contractility in-vitro.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| Parameter measured | **RESPONSE** | **PREGNANCY STATUS** | **REFERENCE** |
|  |  |  |  |
| Advanced Maternal Age |  |  |  |
|  |  |  |  |
| Spontaneous contractility | Decreased | Non-pregnant | Arrowsmith et al. 2012 |
|  | Decreased | Term pregnant | Smith et al. 2008 |
|  | No change | Term pregnant | Arrowsmith et al. 2012  Crankshaw et al. 2015 |
|  |  |  |  |
| K+ depolarisation | Decreased | Non-pregnant | Arrowsmith et al. 2012 |
|  | No change | Term pregnant | Arrowsmith et al. 2012  Crankshaw et al. 2015 |
|  |  |  |  |
| OT response | No change | Term pregnant | Arrowsmith et al. 2012  Crankshaw et al. 2015 |
|  |  |  |  |
| Multiphasic contractions | Increased | Term pregnant | Smith et al. 2008 |
|  |  |  |  |
| Myocyte loss | None | Term pregnant | Sweeney et al. 2013 |
|  |  |  |  |
| KATP expression | Decreased | Term pregnant | Du et al. 2013 |
|  |  |  |  |
|  |  |  |  |
| Obesity |  |  |  |
|  |  |  |  |
| Spontaneous contractility | Decreased | Term pregnant | Zhang et al. 2007 |
|  | No change | Term pregnant | Higgins et al. 2010 |
|  |  |  |  |
| OT response | No change | Term pregnant | Higgins et al. 2010 |
|  |  |  |  |
| OT receptor expression | No change | Term pregnant | Grotegut et al. 2013 |
|  | Increased | Term pregnant | Garabedian et al. 2013 |
|  |  |  |  |
| Connexin 43 expression | Decreased | Term pregnant | Cluff et al. 2006 |
|  | No change | Term pregnant | Garabedian et al. 2013 |
|  |  |  |  |
| h-ERG channel β-inhibitory protein | Decreased | Term pregnant | Parkington et al. 2014 |
|  |  |  |  |
| p160 ROCK-1 expression | Decreased | Term pregnant | O’Brien et al. 2013 |
|  |  |  |  |
| Myocyte loss | Yes | Term pregnant | Gam et al. 2017 |
|  | None | Term pregnant | Sweeney et al. 2013 |
|  |  |  |  |
| Visfatin response | Decreased | Term pregnant | Mumtaz et al. 2015 |
|  |  |  |  |
| Leptin response | Decreased | Term pregnant | Moynihan et al. 2006  Mumtaz et al. 2015 |
|  |  |  |  |
| Ghrelin response | Decreased | Term pregnant | Hehir et al. 2008 |
|  |  |  |  |
| Apelin response | Decreased | Term pregnant | Hehir & Morrison, 2012 |
|  |  |  |  |
|  |  |  |  |
| Diabetes |  |  |  |
|  |  |  |  |
| Spontaneous contractility | Decreased | Term pregnant | Al-Qahtani et al. 2012 |
|  | Unstable over time | Term pregnant | Kaya et al. 1999 |
|  |  |  |  |
| K+ depolarisation | Decreased | Term pregnant | Al-Qahtani et al. 2012 |
|  |  |  |  |
| OT response | No change | Term pregnant | Al-Qahtani et al. 2012 |
|  |  |  |  |
| ET-1 response | Increased | Term pregnant | Kaya et al. 1999 |
|  |  |  |  |