Metabolic Modulation of the Myometrium and Labour, Term and Preterm

M.P. Hehir, J.J. Morrison

Department of Obstetrics & Gynaecology, National University of Ireland Galway, Ireland.

Correspondence at: Professor John J. Morrison, Head of Department, Obstetrics & Gynaecology, National University of Ireland Galway, University Hospital Galway, Newcastle Road, Galway, Ireland.
Tel.: 353 91 493537; Fax: 353 91 494561; E-mail: john.morrison@nuigalway.ie or http://www.nuigalway.ie/obsgyn/

Abstract

An understanding of the physiological and pharmacological factors regulating myometrial contractility is essential to development of therapeutic interventions aimed at addressing the clinical disorders associated with labor. Preterm labor and dystocia are the clinical conditions associated with dysfunctional myometrial contractility. Both conditions are seen in increased frequency in the presence of maternal obesity. This review serves to address the role of adipocytokines, secretory products of adipose tissue, on uterine smooth muscle contractility in pregnancy. These adipocytokines include leptin, ghrelin and apelin. The impact of hypercholesterolemia, hyperlipidemia and other conditions associated with obesity such as diabetes mellitus on myometrial contractile performance is also examined.

Key words: **Adipocytokines, cholesterol, dysfunctional labor, hyperlipidemia, myometrium, obesity, preterm labor.**

Introduction

An understanding of the physiological and pharmacological factors regulating myometrial contractility is essential to development of therapeutic interventions aimed at addressing the clinical disorders associated with labor. Myometrial dysfunction leads to adverse clinical outcomes namely preterm labor or dystocia. These conditions impact on fetal outcome and mode of delivery. Both preterm labor and dystocia have been seen with increased frequency in obese parturients. The purpose of this review is to investigate potential mechanisms leading to preterm labor or dystocia in women in high body mass index categories.

Preterm Labor

Preterm labor, and its clinical sequelae, represents the largest challenge in perinatal medicine, from the perspectives of morbidity and economic cost. Preterm labour is the leading cause of adverse perinatal outcome accounting for 75% of perinatal mortality and more than half of long-term morbidity. (McCormick, 1985). Preterm infants have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term. The morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs (Petrou, 2003; 2005). Estimates indicate that in 2005 the costs to the United States of America alone in terms of medical and educational expenditure associated with preterm birth were more than US$ 26.2 billion (Peristats, 2006). In the USA approximately 1 in 8 infants is delivered before 37 completed weeks while in Europe the reported rate of preterm babies is of the order of 5-9% (Martin et al., 2010; Beck, 2010). Current knowledge of the pathophysiology of preterm labor is poor and, as a result, measures to prevent preterm labour have been largely unsuccessful. Previously described causes include spontaneous preterm labor (31-50%), multiple pregnancy and associated complications (12-28%), preterm prelabor rupture of membranes (6-40%), hypertensive disorders of pregnancy (12%), intrauterine growth restriction (2-4%), ante partum haemorrhage (6-9%) and a small

contribution from anatomical abnormalities (8-9%) (Slattery, 2002).

Epidemiological studies have identified a number of risk factors including low socioeconomic status, black race, extremes of maternal age, multiple pregnancy, low maternal BMI, maternal nutritional status, substance misuse and infection (Goldenberg, 2008). It is, however, often difficult to establish causality in many of these associations due to confounding variables. The molecular and cellular processes involved in the onset and maintenance of human parturition are complex and incompletely understood. Many of the important physiological pathways, associated with onset of the labour process, have been elucidated in studies in recent years (Aguilar and Mitchell, 2010; Arthur et al., 2007; Lopez, 2003) and although some of these mechanisms are reasonably well understood the exact pathophysiology that underlies preterm labour remains unknown (Menon, 2008).

In the last two decades significant research resources have been dedicated to elucidation of the molecular and physiological aspects of uterine function. As a result, our understanding of myometrial contractility, and its regulatory factors, has greatly improved. These extensive efforts have however not yielded results that have made a meaningful impact on either the prevention or treatment of preterm birth, and, sadly, the adverse perinatal outcome has remained unchanged (Costeloe, 2000; Kenyon and Peebles, 2011).

For tocolytic drugs, formerly the mainstay of treatment for preterm labour, recent research findings have established both their clear limitations in terms of benefit, and also highlighted their major adverse maternal and fetal effects (Tsatsaris et al., 2001; Berkman et al., 2003; Anotayanonth et al., 2003; Papatsonis et al., 2005).

Historically, β2 adrenergic agonists had been the most widely used agents in clinical practice (de Heus et al., 2008). In more recent times many newer agents with effects on uterine contractility and efficacy in the maintenance of uterine quiescence have been investigated (Terrone et al., 2000; Bisits et al., 2004; Gill et al., 2006; Conde-Agudelo et al., 2011; Usta et al., 2011). Of these agents, β-mimetics, the oxytocin antagonist atosiban, and the Ca2+ channel blocker, nifedipine, have all been shown to significantly delay delivery after the onset of preterm labour for longer than 24 h and 48 h compared with placebo or no treatment (Romero et al., 2000; Tsatsaris et al., 2001; Wex et al., 2011; Derbent et al., 2011; Nassar et al., 2011). However, neonatal outcome, as measured by perinatal death, respiratory distress syndrome, birthweight, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhages, seizures, hypoglycaemia, or neonatal sepsis did not differ greatly in treatment and control groups.

No definitive tocolytic compound, with the correct balance of efficacy, side-effect profile and positive effect on neonatal outcome, has emerged despite intensive research effort (Kam and Lamont, 2008). For this reason, significant scientific and clinical resources have continued to be invested into the development of novel tocolytic agents (Yuan and Lopez Bernal, 2007; Bourguet et al., 2011). In order to develop these new tocolytics, an improved understanding of the factors governing myometrial physiology is necessary and for this reason the focus of attention in recent years has also moved to endogenous factors regulating myometrial contractility (Crankshaw and Morrison, 2011) alongside the appreciation that metabolic factors play a significant role (Elmes et al., 2011). For these reasons, this chapter will explore the potential role of metabolic factors in regulation of myometrial contractility, and analyse the relevance of extremes of body mass index, particularly obesity, and other metabolic states, to the timing and control of parturition.

Obesity and Dystocia

Obesity is an increasing challenge in obstetric practice. The physical and metabolic sequelae of obesity are associated with a large number of pregnancy and delivery related complications (Weiss et al., 2004; Ovesen et al., 2011). It is also evident that the prevalence and extent of obesity in women of childbearing age has increased in recent years (Kanaglingam et al., 2005; Lynch et al., 2008). Increased BMI makes practical clinical procedures such as clinical examination, phlebotomy and intravenous cannulation challenging. There is also an increasing body of evidence to suggest that obesity plays a role in adverse fetal conditions such as neural tube defects, congenital heart defects, stillbirth, intrauterine growth restriction and macrosomia (Abrams and Laros et al., 1986; Seidman et al., 1989; Jensen et al., 2003; Arendas et al., 2008; Rasmussen et al., 2008; Flenady et al., 2011). Recent studies have shown that intra-partum complications such as dysfunctional labour, increased caesarean delivery, macrosomia, shoulder dystocia and fetal brachial plexus injury are increased in women who are overweight or obese (Weis et al., 2004; Bhattarcarya et al., 2007; Owens et al, 2010). Previous hypotheses have suggested that excessive adipose tissue distribution in the maternal pelvis, or around the fetal shoulders and abdomen, or inadequate maternal effort in the second stage of labor, may be responsible for the dystocic and dysfunctional labour seen in

obese parturients. However the idea that metabolic modulation of uterine contractility may play a role in the dysfunctional labour observed in this group of women has also been raised (Lowe and Corwin, 2011). This theory hypothesizes that women with a higher body mass index are more likely to have metabolic factors contributing to inefficient uterine action, and higher caesarean section rates, all of which have been observed in these women (Weiss et al., 2004).

In recent years much research interest has focused on a new range of secretory products from adipose tissue, collectively known as adipocytokines (Briana and Malamitsi-Puchner, 2010), many of which are now known to be closely linked to metabolic regulation of important systemic factors such as glucose tolerance, insulin resistance, cardiac and vascular function, and many other neuro-endocrine mediated processes (Xu et al., 2010; Torres-Leal et al., 2010). Adipocytokines such as leptin, adiponectin, resistin, ghrelin and apelin have been shown to be implicated in fetal growth and in utero development though their exact role in this complex process must still be completely elucidated (Malamitsi-Puchner et al., 2007; Chanoine et al., 2009; Higgins and Mc Auliffe, 2010). What is conclusive is that serum concentrations of most adipocytokines are altered in the pregnant state and that these compounds are expressed in significant concentrations by the feto - placental unit (Zhao et al., 2004; O'Brien et al., 2010; Van Mieghem et al., 2010). This indicates that adipocytokines play a central role in the development and maintenance of normal pregnancy and may also have an impact on myometrial function. The outline below will examine the effects of adipocytokines, and other metabolic factors, in relation to their effects on myometrial contractility.

Adipocytokines

Leptin

Leptin is a peptide with 167 amino acid residues which is secreted from adipose tissue under the control of the obesity gene (Haynes et al., 1998) and is known to have regulatory effects on neuronal tissue, vascular smooth muscle and non-vascular smooth muscle systems (Yuan et al., 2004). Serum leptin concentrations have been shown to rise significantly with increasing percentage body fat (Considine et al., 1996) and obese individuals have markedly increased leptin production (Hamilton et al., 1995). The role of leptin in human reproduction is not clear. While leptin is most likely involved in the regulation of ovarian function, oocyte maturation, embryo development and implantation (Haynes et al., 1998), the role of leptin during pregnancy has not been clearly established. The placenta is a major source of leptin production during pregnancy (Domali and Messinis, 2002; Zhao et al., 2004), and leptin may play a role in the pathophysiology of preeclampsia (Anderson et al., 2005) and hypertensive disorders of pregnancy (Ozkan et al., 2005). Leptin and leptin receptor genes are also expressed in human umbilical cord, fetal membranes and uterine tissue (Akerman et al., 2002).

In the human (Krizova et al., 2004), as well as in rat (Chien et al., 1997) and higher mammalian models (Wang et al., 2005), serum leptin levels are markedly elevated during pregnancy and demonstrate a significant decrease just before or at the time of parturition.

Leptin has been demonstrated to decrease myometrial contractility in an in vitro model (Moynihan et al., 2006). These findings are demonstrable and similar for both spontaneous and oxytocin induced contractions. This relaxant effect was observed at relatively low concentrations for in vitro experiments and was apparently cumulative in nature. Leptin was found to exert a mean maximal inhibition (MMI) of contractility of 46.794 ± 5.133% (n = 6) on spontaneous myometrial contractions. Figure 1 shows the effect of leptin on spontaneous myometrial contractility in vitro (figure reproduced with permission from Elsevier Science). When this effect was investigated in oxytocin-induced contractions, similar results were seen. Leptin was found to be responsible for a mean maximal inhibition (MMI) of 42.323 ± 3.642 % (n = 6). Both of these inhibitory responses were found to be statistically significant when compared with simultaneously run vehicle controls. This physiological inhibitory effect of leptin on uterine contractility may play a role in the dysfunctional labor process associated with maternal obesity. Furthermore these findings raise the possibility that metabolic factors may play a role in the dysfunctional labours seen in women in high BMI categories.

Ghrelin

Ghrelin is a 28-amino acid peptide and is the endogenous ligand for the growth hormone secretagogue receptor. It is centrally involved in the control of food intake, energy balance and utilization of fat during pregnancy (Budak et al., 2006). When first described,it was thought that, ghrelin was produced predominantly in the stomach (Kojima et al., 1999) However it is now reported that ghrelin production takes place in many other tissues including the placenta, ovary, and testis, of both rats and humans (Gualillo et al., 2001; Gaytan et al., 2005). In human

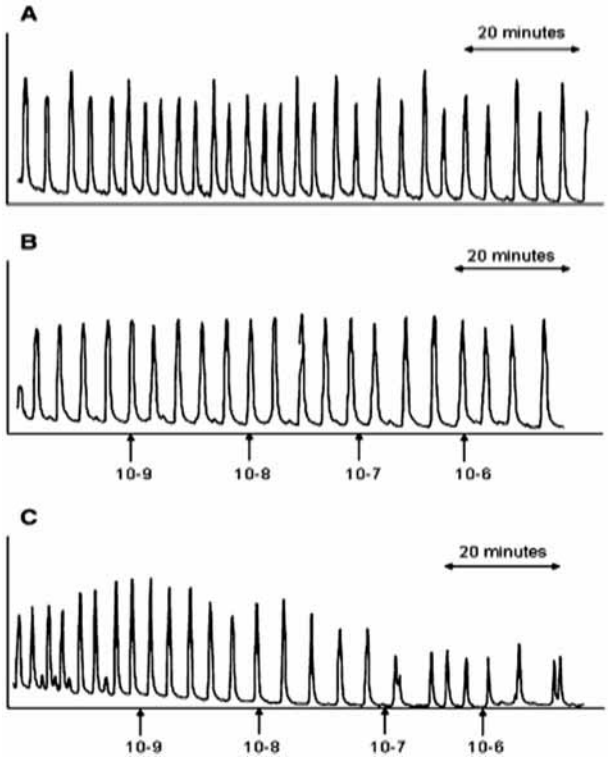

Fig. 1. — Effects of leptin on spontaneous myometrial contractility in pregnant nonlaboring tissue. Representative recordings demonstrating **A**, spontaneous contractions in a control strip, **B**, spontaneous contractions treated with vehicle only, and **C**, the effects of cumulative additions of leptin (1 nmol/l-1 μmol/L) in 20-minute intervals are shown.

pregnancy it is established that serum ghrelin levels peak around mid-gestation and fall to their lowest levels in the third trimester (Fuglsang et al., 2005). In general, ghrelin levels are reduced in obese non-pregnant adults, but are increased in subjects (adults and children), of low body mass index (Soriano-Guillen et al., 2004).

In an in vitro setting ghrelin has been shown to exert an influence on uterine contractility (Hehir et al., 2008). Ghrelin was found to exert an inhibitory effect on contractility, compared to simultaneously run control strips. The mean maximal inhibition values were found to be 33.66 ± 2.63% for spontaneous contractions ($n = 6$; $P < 0.05$), and 31.55 ± 4.64% for oxytocin-induced contractions ($n = 6$; $P < 0.05$).

This inhibitory effect of ghrelin on uterine contractions suggests it plays a physiologic role in regulation of myometrial activity. This is consistent with the low levels of ghrelin, which are observed in the third trimester. These results highlight the potential role of metabolic modulation of myometrium, and particularly at extremes of BMI measurements.

Apelin

Apelin is an adipocytokine, which is a novel bioactive peptide identified as the endogenous ligand of the orphan G protein-coupled receptor, APJ (Tatemoto et al., 1998). The physiologically active apelin molecule is a 36 amino-acid peptide. In humans it is secreted by many systems such as vascular smooth muscle, pituitary and pancreatic tissues (Brailoiu et al., 2002; Ringström et al., 2010; Maenhaut and Van de Voorde, 2011). Apelin has also been shown to be expressed in the placenta (Van Mieghem, 2010), however it is primarily expressed by adipose tissue and serum levels are found to be increase in the obese state (Boucher et al., 2055). Serum apelin levels are also found to decrease in a fasting state and increase upon re-feeding, suggesting that insulin may regulate apelin gene expression and secretion.[81] Physiologically apelin has also been shown to be involved in the regulation of cardiovascular function and fluid homeostasis (Reaux et al., 2001; Quazi et al., 2009;). Serum apelin levels have been shown to be decreased in the second trimester of pregnancy compared with non-pregnant controls however fetal levels have been shown to be markedly increased on Day 1 and Day 4 of life (Malamitsi-Puchner et al., 2007; Kourtis et al., 2011).

We have demonstrated that apelin exerts a relaxant effect on human myometrial contractility in vitro (Hehir and Morrison, 2012). A mean maximal inhibition in contractility (MMI) of 36.8% ± 6.4 was recorded in spontaneous contractions ($n = 6$) ($P < 0.05$). In the case of agonist - induced contractions a mean maximal inhibition (MMI) of 30.4% ± 4.6 ($n = 6$) ($P < 0.05$) was recorded. Similar to other adipocytokines apelin has been found to exert an inhibitory effect on human myometrial contractility in vitro, in tissue obtained during pregnancy. The cellular mechanisms of this, however, and the potential clinical implications, are not fully clear. However, these findings in addition to those mentioned previously further contribute to the concept of metabolic regulation of human myometrial function during pregnancy.

Cholesterol and Lipids

During pregnancy, complex changes occur in lipid profiles. From the 12th week of gestation, phospholipids, cholesterol (total, LDL, HDL), and triglycerides increase in response to estrogen stimulation and insulin resistance (Piechota and Staszewski, 1992; Toescu et al., 2004; Ghio et al., 2011). These changes in lipid balance have been suggested to provide anabolic support for the fetus. In a fasting maternal state adipose tissue lipolytic activity is highly enhanced, and its products, free fatty acids (FFA) and glycerol, are mainly driven to maternal liver, where FFA are converted to ketone bodies and

glycerol to glucose, which easily cross the placenta and sustain fetal metabolism (Herrera, 2002). Recent work has suggested that these alterations affect lipid rafts and caveolae (the omega-shaped invaginations of cell membranes found in uterine smooth muscle, which are stabilized by the cholesterol- binding protein caveolin) and thereby uterine signalling cascades and contractility (Smith et al., 2005). Cholesterol, an essential component of caveolae, has also been shown to have an important role in controlling smooth muscle contractility (Dreja et al., 2002; Noble et al., 2006). Body mass index and hypercholesterolemia have been shown to be positively associated (Gostynski et al., 2004). There is also evidence that cholesterol levels are particularly raised in obese pregnant women's serum (Podedinsky, 1987) and in the membranes of obese pregnant women's myometrium (Pulkkinen et al., 1998).

In an *in vitro* model both cholesterol was found to decrease both the amplitude and the amount of force produced in unit time of spontaneous myometrial contractility. This relaxant effect was also seen in contractions elicited with the addition of oxytocin. These contractile changes are related to changes in intracellular calcium (Jie Zhang et al., 2007). The elevated cholesterol seen in pregnancy may therefore contribute to uterine quiescence prior to parturition but could cause difficulties in labor in obese and/or dyslipidemic women, consistent with their increased cesarean delivery rates.

Obesity

As alluded to above women with a raised BMI have been shown to have an increased rate of caesarean section (Weiss et al., 2004). The increased rate of caesarean section seen in this group of parturient has been shown to be mainly due to a failure in the progression of the labour in the first stage (Crane et al., 1997; Young and Woodmansee, 2002). Recent studies have also demonstrated that obese women delivering vaginally are at increased risk of prolonged first stage of labour and that overweight and obese women had a significantly slower labour progression before 7-cm dilation and an increased rate of first-stage caesarean section (Vahratian et al., 2004). Myometrium from obese women has been shown, in an *in vitro* model, to contract with less force and frequency than that from normal-weight women. Measurements of intracellular calcium indicate that alterations in calcium are responsible for these changes in contractility (Zhang et al., 2007) increased rates of post - partum haemorrhage was also seen in this group of parturients and this is consistent with the hypothesis posed, namely that inadequate uterine activity is associated with obesity. In addition to these findings obesity has been shown to alter the properties of the feto-placental vasculature, namely by affecting the tone of the umbilical artery in vitro (Hehir et al., 2009). These results have implications for fetal growth and development in utero.

Diabetes Mellitus

Diabetes in pregnancy is associated with significant fetal and maternal morbidity and mortality. The rate of caesarean section is higher in women with diabetes (Ehrenberg et al., 2004; Jensen et al., 2004), with the Confidential Enquiry into Maternal and Child Health reporting a rate of 67.4% (Department of Health, 2010). Caesarean section in women with diabetes in pregnancy is associated with a 2.5-fold increased risk of wound infection (Takoudes et al., 2004), and an increased risk of thrombosis and postpartum haemorrhage (Dunne et al., 2003). Despite the significant morbidity associated with CS in diabetic pregnancies, the high CS rate in diabetic pregnancies is not understood. Some authors suggest that the increased CS rate is due to the confounding factor of obesity (Langer et al., 2005), however, other analyses have found diabetes mellitus to be an independent risk for CS (Bo et al., 2003; Kjos et al., 2004). Although macrosomia has been reported as a risk factor for cesarean delivery studies have found that a reduction in macrosomia does not result in a concomitant reduction in CS rate (Crowther et al., 2005). Recent studies analysing the contractile performance of myometrium from diabetic mothers versus that of non-diabetic women have shown that there is significantly decreased contraction amplitude and duration in myometrium from diabetic compared with control patients, even when possible confounders such as BMI were analysed (Al-Qahtani et al., 2012). Reduced intracellular calcium signals and expression of calcium channels were found in uteruses from diabetic patients, which, along with a reduction in muscle content found on histological examination, could explain these findings. In the presence of oxytocin myometrium from diabetic patients did not reach the levels found in non-diabetic patients (Al Qahtani et al., 2012). These findings may well contribute to the increased emergency caesarean section rate seen in diabetic mothers.

Conclusion

The complications associated with obesity in an obstetric population have been widely reported. The hypothesis that a woman's metabolism may have an effect on her ability to labor successfully is novel and

by no means fully elucidated. Previous studies have suggested that dysfunctional labors seen in women from increased BMI categories were due to cephalopelvic disproportion secondary to increased pelvic soft tissue (Young and Woodmansee, 2002), however the increasing evidence outlined in this review would suggest that physiology and endocrinology also play a role in this process.

The adipocytokines are a particularly interesting group of compounds which may well hold potential in unlocking the reasoning for the poor labor performance of obese women. The adipocytokines were all found to have an effect on myometrial contractility in vitro and this increases the evidence in favour of metabolic modulation of uterine smooth muscle contractility. The exact mechanism by which these compounds cause their effect on contractile performance are hitherto, however, uninvestigated. This is an area with potential for future investigation, as is the discovery, and examination of the effects, of more novel products of adipose tissue on myometrial contractility. Novel adipocytokines which are altered in accordance with BMI include adiponectin (Arita et al., 1999), and visfatin (Fukuhara et al., 2005) and these compounds may provide grounds for future research.

Cholesterol and other lipids are altered during the pregnant state, however in the presence of obesity this increase can be exaggerated and may lead to increased serum concentrations which may in turn influence uterine contractility. The mechanism of this action is clearer and can be attributed to alterations in intracellular calcium.

The presence of metabolic states such as obesity and diabetes mellitus have been shown to influence myometrial contractility in an in vitro model and this suggests that education about these conditions and decreasing their incidence may benefit people in labour, the exact mechanism whereby these conditions exert their effects remain unclear but the in vitro findings are in broad agreement with the suggestion that obese and diabetic women labour poorly leading to a much higher caesarean section rate in this patient group. In conclusion, this review provides valuable insight into the potential for metabolic modulation to influence myometrial activity and hence labour outcome, but this is a novel area of research, and one which still poses many questions to be addressed in the future.

References

Abrams B, Laros R Jr: Prepregnancy weight, weight gain, and birth weight. Am J Obstet Gynaecol. 1986, 154:503-9.

Aguilar H, Mitchell B. Physiological pathways and molecular mechanisms regulating uterine contractility. Hum Reprod Update. 2010;16(6):725-44.

Akerman F, Lei Z, Rao C. Human umbilical cord and fetal membranes co-express leptin and its receptor genes. Gynecol Endocrinol. 2002;16(4):299-306

Al-Qahtani S, Heath A, Quenby S et al. Diabetes is associated with impairment of uterine contractility and high Caesarean section rate. Diabetologia. 2012 ;55(2):489-98.

Anderson C, Lopez F, Zhang H et al. Characterization of changes in leptin and leptin receptors in a rat model of preeclampsia. Am J Obstet Gynecol. 2005;193(1):267-72.

Anotayanonth S, Subhedar N, Garner P et al. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004352.

Arendas K, Qiu Q, Gruslin A. Obesity in pregnancy: preconceptional to postpartum consequences. J Obstet Gynaecol Can. 2008;30(6):477-88.

Arita Y, Kihara S, Ouchi N et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257:79-83.

Arthur P, Taggart M, Mitchell B. Oxytocin and parturition: a role for increased myometrial calcium and calcium sensitization? Front Biosci. 2007;12:619-33.

Beck S, Wojdyla D, Say L et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010;88(1):31-8.

Berkman N, Thorp J Jr, Lohr K et al. Tocolytic treatment for the management of preterm labor: a review of the evidence. Am J Obstet Gynecol. 2003;188(6):1648-59.

Bhattacharya S, Campbell D, Liston W et al. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health. 2007;7:168.

Bisits A, Madsen G, Knox M et al. The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. Am J Obstet Gynecol. 2004;191(3):683-90.

Bo S, Menato G, Signorile A et al. Obesity or diabetes: what is worse for the mother and for the baby? Diabetes Metab. 2003;29:175-8.

Boucher J, Masri B, Daviaud D et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology. 2005;146(4):1764-71.

Bourguet C, Goupil E, Tassy D et al. Targeting the prostaglandin F2α receptor for preventing preterm labor with azapeptide tocolytics. J Med Chem. 2011;54(17):6085-97.

Brailoiu G, Dun S, Yang J et al. Apelin-immunoreactivity in the rat hypothalamus and pituitary. Neurosci Lett. 2002;327(3): 193-7.

Briana D, Malamitsi-Puchner A. The role of adipocytokines in fetal growth. Ann N Y Acad Sci. 2010;1205:82-7.

Budak E, Fernandez Sanchez M, Bellver J et al. Interactions of the hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. Fertil Steril. 2006; 85(6):1563-81.

Chanoine J, De Waele K, Walia P. Ghrelin and the growth hormone secretagogue receptor in growth and development. Int J Obes (Lond). 2009;33 Suppl 1:S48-52.

Chien E, Hara M, Rouard M et al. Increase in serum leptin and uterine leptin receptor messenger RNA levels during pregnancy in rats. Biochem Biophys Res Commun. 1997;237: 476-80.

Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: a systematic review and meta-analysis. Am J Obstet Gynecol. 2011;204(2):134.e1-20.

Considine R, Sinha M, Heiman M et al. Serum immunoreactive leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334:292-5.

Costeloe K, Hennessy E, Gibson A et al. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics. 2000;106:659-71.

Crane S, Wojtowycz M, Dye T et al. Association between prepregnancy obesity and the risk of cesarean delivery. Obstet Gynecol. 1997;89:213-6.

Crankshaw D, Morrison J. Methodology and pharmacological analysis of effects of uterotonic compounds in human

myometrium in vitro. Am J Obstet Gynecol. 2011;205(2): 155.e1-6.
Crowther C, Hiller J, Moss Jet al. . Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352:2477-86.
de Heus R, Mulder EJ, Derks JB et al. Acute tocolysis for uterine activity reduction in term labor: a review. Obstet Gynecol Surv. 2008;63(6):383-8.
Department of Health (2010) NHS Maternity Statistics, England. 2002-2003 Statistical Bulletin.
Derbent A, Simavli S, Gümüş II et al. Nifedipine for the treatment of preterm labor in twin and singleton pregnancies. Arch Gynecol Obstet. 2011;284(4):821-6.
Domali E, Messinis I. Leptin in pregnancy. J Matern Fetal Neonatal Med. 2002;12(4):222-30.
Dreja K, Voldstedlund M, Vinten J et al. Cholesterol depletion disrupts caveolae and differentially impairs agonist-induced arterial contraction. Arterioscler Thromb Vasc Biol. 2002; 22(8):1267-72.
Dunne F, Brydon P, Smith K et al. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990-2002. Diabet Med. 2003;20:734-8.
Ehrenberg H, Durnwald C, Catalano P et al. The influence of obesity and diabetes on the risk of cesarean delivery. Am J Obstet Gynecol. 2004;191:969-74.
Elmes M, Tan D, Cheng Z et al. The effects of a high-fat, high-cholesterol diet on markers of uterine contractility during parturition in the rat. Reproduction. 2011;141(2):283-90.
Flenady V, Koopmans L, Middleton P et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet. 2011;377(9774):1331-40.
Fuglsang J, Skjaerbaek C, Espelund U et al. Ghrelin and its relationship to growth hormones during normal pregnancy. Clin Endocrinol. 2005;62:554-9.
Fukuhara A, Matsuda M, Nishizawa M et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307:426-30.
Gaytan F, Barreiro M, Chopin L et al. Immunolocalization of ghrelin and its functional receptor, the type Ia growth hormone secretagogue receptor, in the cyclic human ovary. J Clin Endocrinol Metab. 2005;90(3):1798-1804.
Ghio A, Bertolotto A, Resi V et al. Triglyceride metabolism in pregnancy. Adv Clin Chem. 2011;55:133-53.
Gill A, Madsen G, Knox M et al. Neonatal neurodevelopmental outcomes following tocolysis with glycerol trinitrate patches. Am J Obstet Gynecol. 2006;195(2):484-7.
Goldenberg R, Culhane J, Iams J et al. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
Gostynski M, Gutzwiller F, Kuulasmaa K, et al. Analysis of the relationship between total cholesterol, age, body mass index among males and females in the WHO MONICA Project. Int J Obes Relat Metab Disord. 2004;28(8):1082-90.
Gualillo O, Caminos J, Blanco M et al. Ghrelin a novel placental-derived hormone. Endocrinology. 2001;142(2) :788-94.
Hamilton B, Paglia D, Kwan AYM et al. Increased obese mRNA expression in omental fat cells from massively obese humans. Nat Med.1995;1:953-6
Haynes W, Morgan D, Walsh S et al. Cardiovascular consequences of obesity: role of leptin. Clin Exp Pharmacol Physio. 1998;25(1):65-9.
Hehir M, Glavey S, Morrison J. Uterorelaxant effect of ghrelin on human myometrial contractility. Am J Obstet Gynecol. 2008;198(3):323.e1-5.
Hehir M, Morrison J. The adipokine apelin and human uterine contractility. Am J Obstet Gynecol. 2012;206(4):359.e1-5.
Hehir M, Moynihan A, Glavey S et al. Umbilical artery tone in maternal obesity. Reprod Biol Endocrinol. 2009;7:6.
Herrera E. Implications of dietary fatty acids during pregnancy on placental, fetal and postnatal development – a review. Placenta. 2002;23 Suppl A:S9-19.
Higgins M, Mc Auliffe F. A review of maternal and fetal growth factors in diabetic pregnancy. Curr Diabetes Rev. 2010;6(2): 116-25.
Jensen D, Damm P, Moelsted-Pedersen L et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care. 2004; 27:2819-23.
Jensen D, Damm P, Sorensen B et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. Am J Obstet Gynecol. 2003;189(1):239-44.
Jie Zhang, Kendrick A, Quenby S et al. Contractility and calcium signaling of human myometrium are profoundly affected by cholesterol manipulation: implications for labor? Reprod Sci. 2007;14(5):456-66.
Kam K, Lamont R. Developments in the pharmacotherapeutic management of spontaneous preterm labor. Expert Opin Pharmacother. 2008;9(7):1153-68.
Kanaglingam M, Forouhi N, Greer I et al. Changes in booking BMI over a decade: retrospective analysis from a Glasgow Maternity Hospital. BJOG. 2005;112(10):1431-3.
Kenyon A, Peebles D. Myth: tocolysis for prevention of preterm birth has a major role in modern obstetrics. Semin Fetal Neonatal Med. 2011;16(5):242-6.
Kjos S, Berkowitz K, Xiang A. Independent predictors of cesarean delivery in women with diabetes. J Matern Fetal Neonatal Med. 2004;15:61-7.
Kojima M, Hosoda H, Date Y et al. Ghrelin is a growth-hormone releasing acetylated peptide from the stomach. Nature. 1999; 402:656-60.
Kourtis A, Giomisi A, Mouzaki M et al. Apelin levels in normal pregnancy. Clin Endocrinol (Oxf). 2011;164(4):579-83.
Krizova J, Eretova V, Haluzikova D et al. Soluble leptin receptor and leptin levels in pregnant women before and after delivery. Endocr Res. 2004;30(3):379-85.
Langer O, Yogev Y, Xenakis EM et al. Overweight and obese in gestational diabetes: the impact on pregnancy outcome. Am J Obstet Gynecol. 2005;192:1768-76.
López Bernal A. Mechanisms of labour – biochemical aspects. BJOG. 2003;110 Suppl 20:39-45.
Lowe N, Corwin E. Proposed biological linkages between obesity, stress, and inefficient uterine contractility during labor in humans. Med Hypotheses. 2011;76(5):755-60.
Lynch C, Sexton D, Hession M et al. Obesity and mode of delivery in primigravid and multigravid women. Am J Perinatol. 2008;25(3);163-7.
Maenhaut N, Van de Voorde J. Regulation of vascular tone by adipocytes. BMC Med. 2011;9:25. Review.
Malamitsi-Puchner A, Gourgiotis D, Boutsikou M et al. Circulating apelin concentrations in mother/infant pairs at term. Acta Paediatr. 2007;96(12):1751-4.
Martin J, Osterman M, Sutton P. Are preterm births on the decline in the United States? Recent data from the National Vital Statistics System. NCHS data brief, no 39. Hyattsville, MD: National Center for Health Statistics. 2010.
McCormick, M. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med. 1985; 312:82-90.
Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta Obstet Gynecol Scand. 2008;87(6):590-600.
Moynihan A, Hehir M, Glavey S et al. Inhibitory effect of leptin on human uterine contractility in vitro. Am J Obstet Gynecol. 2006;195(2):504-9.
Nassar A, Aoun J, Usta I. Calcium channel blockers for the management of preterm birth: a review. Am J Perinatol. 2011;28(1):57-66.
Noble K, Zhang J,Wray S. Lipid rafts, the sarcoplasmic reticulum and uterine calcium signalling: an integrated approach. J Physiol. 2006;570(pt 1):29-35.
O'Brien M, Earley P, Morrison J et al. Ghrelin in the human myometrium. Reprod Biol Endocrinol. 2010;28;8:55.
Ovesen P, Rasmussen S, Kesmodel U. Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. Obstet Gynecol. 2011;118:305-12.
Owens L, O'Sullivan E, Kirwan B et al. ATLANTIC DIP Collaborators. ATLANTIC DIP: the impact of obesity on

pregnancy outcome in glucose-tolerant women. Diabetes Care. 2010;33(3):577-9.
Ozkan S, Erel C, Madazli et al. Serum leptin levels in hypertensive disorder of pregnancy. Eur J Obstet Gynecol Reprod Biol. 2005;120(2):158-63.
Papatsonis D, Flenady V, Cole S et al. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004452.
PeriStats [online database]. White Plains, NY: March of Dimes; 2006.
Petrou S, Mehta Z, Hockley C et al. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics. 2003; 112:1290-7.
Petrou S. The economic consequences of preterm birth during the first 10 years of life. BJOG. 2005;112 Suppl 1:10-5.
Piechota W, Staszewski A. Reference ranges of lipids and apolipoproteins in pregnancy. Eur J Obstet Gynecol Reprod Biol. 1992;45:27-35.
Podedinsky N. Serum lipid composition in obese pregnant patients. Akusherstvo I Ginekologiia Moskva. 1987;6:22-6.
Pulkkinen M, Nyman S, Hamalainen MM et al. Proton NMR spectroscopy of the phospholipids in human uterine smooth muscle and placenta. Gynecol Obstet Invest. 1998;46(4):220-4.
Quazi R, Palaniswamy C, Frishman WH. The emerging role of apelin in cardiovascular disease and health. Cardiol Rev. 2009;17(6):283-6.
Rasmussen S, Chu S, Kim S, et al. Maternal obesity and risk of neural tube defects: a metaanalysis. Am J Obstet Gynecol. 2008;198:611-9.
Reaux A, De Mota N, Skultetyova I, et al. Physiological role of a novel neuropeptide, apelin, and its receptor in the rat brain. J Neurochem. 2001;77(4):1085-96.
Ringström C, Nitert M, Bennet H et al. Apelin is a novel islet peptide. Regul Pept. 2010 ;162(1-3):44-51.
Romero R, Sibai B, Sanchez-Ramos L et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obstet Gynecol. 2000;182: 1173-83.
Seidman D, Ever-Hadani P, Gale R. The effect of maternal weight gain in pregnancy on birth weight. Obstet Gynecol. 1989;74(2):240-6.
Slattery M, Morrison J, Preterm delivery. Lancet. 2002; 360(9344):1489-97.
Smith R, Babiychuk E, Noble K et al. Increased cholesterol decreases uterine activity: functional effects of cholesterol alteration in pregnant rat myometrium. Am J Physiol Cell Physiol. 2005;288(5):C982-8.
Soriano-Guillen L, Barrios V, Campos-Baros A et al. Ghrelin levels in obesity and anorexia nervosa: effect of weight reduction or recuperation. J Pediatr. 2004;144:36-42.
Takoudes T, Weitzen S, Slocum J et al. Risk of cesarean wound complications in diabetic gestations. Am J Obstet Gynecol. 2004;191:958-63.
Tatemoto K, Hosoya M, Habata Y et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun. 1998;251(2): 471-6.
Terrone D, Rinehart B, Kimmel E et al. A prospective randomized, controlled trial of high and low maintenance doses of magnesium sulfate for acute tocolysis. Am J Obstet Gynecol. 2000;182:1477-82.
Toescu V, Nuttall S, Martin U et al. Changes in plasma lipids and markers of oxidative stress in normal pregnancy and pregnancies complicated by diabetes. Clin Sci (Colch). 2004; 106:93-8.
Torres-Leal F, Fonseca-Alaniz M, Rogero M et al. The role of inflamed adipose tissue in the insulin resistance. Cell Biochem Funct. 2010;28(8):623-31.
Tsatsaris V, Papatsonis D, Goffinet F et al. Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. Obstet Gynecol. 2001;97:840-7.
Usta I, Khalil A, Nassar A. Oxytocin antagonists for the management of preterm birth: a review. Am J Perinatol. 2011; 28(6):449-60.
Vahratian A, Zhang J, Troendle J et al. Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. Obstet Gynecol. 2004;104:943-51.
Van Mieghem T, van Bree R, Van Herck E et al. Maternal apelin physiology during rat pregnancy: the role of the placenta. Placenta. 2010;31(8):725-30.
Wang C, Medan M, Shimizu K et al. Secretion of leptin throughout pregnancy and early postpartum period in Japanese monkeys: placenta as another source of leptin. Endocrine. 2005;27(1):75-82.
Weiss J, Malone F, Emig D et al. Obesity, obstetric complications and cesarean delivery rate – A population-based screening study. Am J Obstet Gynecol. 2004;190:1091-7.
Wex J, Abou-Setta A, Clerici G et al. Atosiban versus beta-mimetics in the treatment of preterm labour in Italy: clinical and economic importance of side-effects. Eur J Obstet Gynecol Reprod Biol. 2011;157(2):128-35. Review.
Xu A, Wang Y, Lam K et al. Vascular actions of adipokines molecular mechanisms and therapeutic implications. Adv Pharmacol. 2010;60:229-55. Review.
Xu S, Tsao P, Yue P. Apelin and insulin resistance: another arrow for the quiver? J Diabetes. 2011;3(3):225-31.
Young T, Woodmansee B. Factors that are associated with cesarean delivery in a large private practice: the importance of prepregnancy body mass index and weight gain. Am J Obstet Gynecol. 2002;187:312-8
Yuan S, Chung Y, Chen H et al. Aberrant expression and possible involvement of the leptin receptor in bladder cancer. Urology. 2004;63:408-13.
Yuan W, López Bernal A. Cyclic AMP signalling pathways in the regulation of uterine relaxation. BMC Pregnancy Childbirth. 2007;7 Suppl 1:S10. Review
Zhang J, Bricker L, Wray S et al. Poor uterine contractility in obese women. BJOG. 2007;114(3):343-8.
Zhao J, Townsend K, Schulz L et al. Leptin receptor expression increases in placenta, but not hypothalamus, during gestation in Mus musculus and Myotis lucifungus. Placenta. 2004; 25:712-22.