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Mother Nature versus Father Time

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In high-income countries, the average age at which women are giving birth to their first child has increased steadily in recent years. Lifestyle appears to be a major factor involved in postponing parenthood (Waldenstrom, 2016), until Mother Nature comes calling in the mid 30's and later. However, in the intervening years Father Time has been busy, a decline in fertility has developed and, if pregnancy occurs, there is an increased risk of adverse outcomes. Advanced maternal age, especially for first-time mothers, has a significant adverse impact on maternal and perinatal morbidity. The risk of stillbirth is markedly increased with maternal age, especially in women giving birth for the first time (Waldenstrom *et al.*, 2015) (1.8 million Swedish women). Advancing maternal age is also associated with an increase in the incidence of caesarean section (CS), gestational diabetes, gestational hypertension, preeclampsia, placenta praevia, and prolonged hospital care (Klemetti *et al.*, 2016). In women over 35 years of age in spontaneous labour the need for augmentation, that is, oxytocin infusion to strengthen contractions, was approximately double that of women of 20-24 years (Omih & Lindow, 2016) (30,000 British women) (Figure 1). In the same study, delivery was more likely to be by CS in women in the older age group (>35 years). The need for augmentation and CS was particularly evident for older first-time pregnancies compared with older women who had previously given birth (Figure 1). Failure to progress in labour is often associated with dysfunctional uterine contraction, and is the most common indication for primary CS, accounting for 50% of CS in nulliparous women and for the majority of repeat CS in labour (Ragusa *et al.*, 2016). It has been suggested that poor uterine contractile function may be responsible for the slow labour, increased need for CS, and increased post-partum haemorrhage reported in the labour of first-pregnancy women over 40 years of age (Bianco *et al.*, 1996; Ziadeh & Yahaya, 2001).

The incidence of dysfunctional labour with poor uterine contractile function has increased in recent years alongside an overall increase in the CS rate. This is significant in medical and economic terms.

Obese pregnant women have higher rates of prolonged labour, as diagnosed by slower cervical dilation necessitating labour augmentation and higher rates of CS (Nuthalapaty *et al.*, 2004; Ramachenderan *et al.*, 2008). However, dysfunctional labour is also affected by maternal age. In the current issue, Patel *et al.* have made a careful and detailed study of the effect of maternal age on pregnancy outcomes in mice. These mice were primiparous and at an age equivalent to approximately 35 years in humans. They report prolonged pregnancy length and labour duration in older mice. Oxytocin receptor and connexin-43 mRNA expression were reduced, myometrial responsiveness to oxytocin was blunted, and the normal strong contractions in uterine strips from these mice were replaced by high-frequency, low-amplitude contractions. Combined, these characteristics would be expected to result in "dysfunctional labour" and likely explain the poor labour performance and the elevated incidence of stillbirths observed in that study, as is the case for advanced maternal age in women. Pregnancy outcomes have also been studied in first-time pregnant aged rat dams. Compared with young counterparts, there was evidence of placental insufficiency, reduced contractile activity in uterine wall and uterine artery smooth muscle, and altered expression of contractile proteins in myometrium (Care *et al.*, 2015; Elmes *et al.*, 2015).

This places the focus on the contractility of uterine smooth muscle. Contraction requires an increase in free cytoplasmic calcium in the smooth muscle, which is regulated by ion channels and signalling systems that include receptors for important hormones (e.g. oxytocin, prostaglandins) and cytoplasmic enzymes that modulate the sensitivity of the contractile apparatus to calcium (e.g. protein kinases C and A, myosin light chain kinase and phosphatase). Coordination of the smooth muscle cells within the uterine wall, required to achieve whole-organ contraction, is accomplished by gap junctions, especially connexin-43, and mechanosensitive ion channels. Throughout pregnancy, the uterus contains the fetus which is "foreign", fetal growth stretches the smooth muscle and both invoke smooth muscle contraction. As a consequence, suppression of inflammation and stretch-induced contraction is fundamental to the maintenance of pregnancy, and progesterone plays a major role in achieving the quiescence required. Then, during labour, vaginal delivery requires strong, co-ordinated uterine contractions, and withdrawal of progesterone is important in achieving this. In many mammals, circulating progesterone levels decline precipitously within days before normal, successful birth, relieving the inhibitory action of the steroid. An intriguing observation is that the pre-labour steep decline in circulating progesterone is delayed in aged mice (Holinka *et al.*, 1979; Patel *et al*. 2017), and this likely accounts, at least in part, for the prolonged labour. It would explain the reduction in expression of the contraction-associated proteins, oxytocin receptors and connexin-43 reported by Patel *et al*. However, circulating progesterone does not decrease in humans before labour onset and the progesterone withdrawal required for the switch from quiescence to strong contractions of uterine smooth muscle is achieved by the nature of the progesterone receptor, PR-A versus PR-B. During most of pregnancy, the long isoform PR-B predominates and its actions on the genome

ensures quiescence, with suppression of pro-inflammatory cytokine, stimulatory receptors (e.g. oxytocin, prostaglandin $F_{2\alpha}$), connexin-43 expression. In the lead-up to labour, expression of the shorter PR-A isoform is enhanced (Mesiano *et al.*, 2002). PR-A inhibits the activity of PR-B. The ensuing pro-inflammation state results in an increase in the production of a contractile myometrium (Menon *et al.*, 2016). The fate of the PR-A/PR-B ratio in the aged human myometrium during labour requires investigation.

Events in the labour ward have repercussions for both the mother and the offspring. Studies on rodents, such as that by Patel *et al.* in this issue, help to shed light on these matters, although we need to remain mindful of the important differences between rodents and humans in relation to labour and the control of uterine contractile function.

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Figure 1: The need to augment contractions and for caesarean delivery in labouring women increased with maternal age and was required much more often in first-time pregnancies. (Data from 30,022 women in the UK, 46% primiparae and 54% multiparae. Compiled from data in Omih and Lindow (2016).