

# Controlling the timing of labour

## *The role of progesterone and prostaglandins*



**Dr Toni Welsh**  
Mothers and Babies  
Research Centre  
University of Newcastle

**Preterm birth is the leading cause of perinatal mortality and morbidities in developed countries, including Australia, with inadequate treatment options for the prevention or treatment of preterm labour.**

Labour and delivery require an intricate series of coordinated events that are poorly understood in women. Our lack of knowledge of the mechanisms that control the transition from a quiescent to a contractile uterine phenotype impedes the development of novel therapeutics for preventing preterm labour and reducing preterm birth rates. The World Health Organisation (WHO) estimates that preterm births (less than 37 completed weeks of gestation) comprise 9.6 per cent

of all worldwide births, which equates to 12.9 million babies delivered preterm each year.<sup>1</sup> While approximately one third of preterm deliveries are indicated for maternal or fetal complications, the remaining two thirds of spontaneous preterm births that result from spontaneous preterm labour and premature preterm rupture of membranes (PPROM) are candidates for interventions that will prevent or stop preterm labour.<sup>2</sup>

Our studies at the Mothers and Babies Research Centre in Newcastle, New South Wales, investigate the regulation of uterine contractility and hormonal interactions that determine the timing of labour onset in women. I received the Ella Macknight Memorial Scholarship from the RANZCOG Research Foundation for 2009-2010 to pursue the role of two key hormones, progesterone and prostaglandins (PGs), in modulating uterine contractility in pregnant women. By better defining the actions of these hormones at a molecular level in the pregnant uterus, we expect to identify much needed new therapeutic targets for the prevention of preterm birth.

### **Mechanisms of progesterone action and functional progesterone withdrawal**

The role of progesterone in suppressing uterine contractility is common to all mammals. Progesterone withdrawal is a crucial event that precedes the onset of labour and is mediated in most species by a decline in systemic progesterone levels, leading to a rise in uterotonin production and labour onset. In women, where parturition is not preceded by changes in circulating progesterone concentrations, there is thought to be a decrease in progesterone responsiveness in the uterus. This loss of responsiveness or 'functional' progesterone withdrawal leads to increased production of prostaglandins (PGs) that stimulate uterine contractions, cervical softening and fetal membrane rupture. The mechanisms that bring

about functional progesterone withdrawal and the parallel increase in PG synthesis in women are largely unknown.

A clear understanding of how progesterone relaxes the pregnant uterus and how its actions are controlled is important, because recent clinical studies have indicated that progestin-based therapeutics reduce the risk of preterm birth when administered prophylactically in women at risk of recurrent preterm labour.<sup>3,4</sup> The benefit of progestin-based therapies is apparent in singleton pregnancies but not in twin or triplet pregnancies, and is not necessarily associated with a decrease in perinatal deaths or improved neonatal outcome. Therapies based on progestin supplementation are not useful for acute tocolysis in women presenting in preterm labour and it is unclear how they exert their benefit considering the already saturating levels of endogenous progesterone present during pregnancy. A greater understanding of the mechanisms of action of progesterone and progesterone receptors (PRs) in the uterus may lead to more targeted methods of maintaining progesterone function as secondary or tertiary inventions for the prevention of preterm labour and preterm birth. Recent research has advanced our understanding of the molecular mechanisms of progesterone withdrawal in women and introduced novel pathways for the suppression of uterine contractility.

Several molecular mechanisms may contribute to functional progesterone withdrawal in the myometrium, including changes in PR isoform expression, changes in PR co-regulator expression and reduced binding of PRs to gene promoters. We have previously shown that advancing gestation and labour onset are associated with changes in PR isoform expression in women. The 'B' receptor isoform is the dominant mediator of progesterone actions, whereas the 'A' isoform suppresses the actions of PR-B, therefore an increase in the PR-A to PR-B ratio reduces progesterone responsiveness. A critical change in the expression of PR isoforms occurs prior to labour onset in women that results in an increase in the PR-A to PR-B ratio in the uterus.<sup>5</sup> Similar results have been reported in the rhesus monkey, indicating that an increasing uterine PR-A to PR-B ratio may be a common pathway for functional progesterone withdrawal in primates. PRs function by controlling gene transcription in target cells, in concert with various steroid receptor co-regulator proteins that can increase or decrease the transcriptional activity of the receptor. The expression of PR co-activators decreases in human and mouse uteri at term and with labour onset.<sup>6</sup> Thus, the changing PR-A/PR-B ratio in the uterus at term is accompanied by alterations in PR co-activator expression that likely further reduce progesterone responsiveness.

Several nuclear receptor co-activators possess histone acetylase activity and regulate PR activity via chromatin remodelling. Acetylation of histones, the protein component of chromatin, creates an 'open' chromatin conformation in which transcription factors are able to access gene promoters and regulate gene transcription; histone acetylation therefore enhances the transcriptional activity of PRs. Histone deacetylase (HDAC) enzymes conversely generate a 'closed' chromatin conformation and reduce PR activity. The levels of histone acetylation decrease in the human and mouse uterus during labour<sup>6</sup>, which would promote progesterone withdrawal. Maintaining histone acetylation, and therefore progesterone activity, is an attractive target for novel tocolytic development. The HDAC inhibitor Trichostatin A (TSA) up-regulates PR-B expression in uterine cells<sup>7</sup>, inhibits contractions in human uterine tissue *in vitro*<sup>8</sup> and delays parturition in mice.<sup>6</sup> HDAC inhibitors also suppress COX-2 expression in human myometrial cells<sup>9</sup> and may therefore prolong pregnancy by increasing progesterone responsiveness and reducing intrauterine PG synthesis. There is clear potential for the use of HDAC inhibitors as tocolytic agents and the effect of these inhibitors on myometrial function is a major focus of our research funded by the RANZCOG Research Foundation.

### Feed-forward interaction between progesterone and prostaglandins at labour

PG production increases in the uterus before and during labour as a consequence of the up-regulation of the key inducible PG-synthetic enzyme, COX-2. While inhibitors of PG synthesis have been trialled and used extensively for the treatment of preterm labour, adverse neonatal outcomes such as patent ductus arteriosus and impaired renal function have limited their usefulness as tocolytic agents. The interaction between progesterone and PGs in the pregnant uterus is poorly understood, although progesterone is known to suppress PG production until shortly before the onset of labour. Support for a role of PGs in triggering progesterone withdrawal in women first came from studies by our group which showed that PGs caused an increase in the PR-A/PR-B ratio in myometrial cells<sup>10</sup>, and similar results have been reported in decidual cells. The resultant increase in the PR-A/PR-B ratio would reduce progesterone responsiveness and increase uterine activity. These findings support the concept of a feed-forward interaction between PGs and progesterone withdrawal in the pregnant uterus. We propose that PGs stimulate a decrease in myometrial progesterone responsiveness, and that progesterone withdrawal in the myometrium leads to rising intrauterine PG production, resulting in a feed-forward mechanism that increases uterine activity and leads to labour onset. Defining the early events that catalyse the activation of this pathway may provide crucial knowledge of the mechanisms that initiate labour onset in women.

### Conclusions

Birth at an early gestational age is a leading contributor to perinatal mortality and morbidities, including acute morbidities such as respiratory distress syndrome and necrotising enterocolitis, as well as long-term morbidities such as cerebral palsy, blindness and hearing loss. Investigating the molecular mechanisms by which progesterone suppresses contractility in myometrial smooth muscle, and the coordination of progesterone and prostaglandin signalling in the pregnant uterus, is an important field of active research, with potential for the development of targets for novel therapeutics that will maintain uterine quiescence and prevent spontaneous preterm labour and preterm birth and reduce adverse neonatal outcomes. With generous support from the RANZCOG Research Foundation, I will be able to make progress towards these goals during the upcoming years.

### References

1. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PFA. The worldwide incidence of preterm birth: a WHO systematic review of maternal mortality and morbidity. *Bull World Health Organ.* 2009; 88:doi:10.2471/BLT.08.062554.
2. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *The Lancet* 2008; 371(9606):75-84.
3. Dodd JM, Flenady VJ, Cincotta R, Crowther CA. Progesterone for the prevention of preterm birth: a systematic review. *Obstet Gynecol.* 2008;112(1):127-34.
4. Calda P. Safety signals of 17-OHP-C use in pregnancy and efficacy in the prevention of preterm birth. *J Matern Fetal Neonatal Med.* 2009; 22(6):540-42.
5. Merlino AA, Welsh TN, Tan H, Yi LJ, Cannon V, Mercer BM, Mesiano S. Nuclear progesterone receptors in the human pregnancy myometrium: evidence that parturition involves functional progesterone withdrawal mediated by increased expression of progesterone receptor-A. *J Clin Endocrinol Metab.* 2007; 92(5):1927-33.
6. Condon JC, Jeyasuria P, Faust JM, Wilson JW, Mendelson CR. A decline in the levels of progesterone receptor coactivators in the pregnant uterus at term may antagonise progesterone receptor function and contribute to the initiation of parturition. *Proc Natl Acad Sci USA* 2003;100(16):9518-23.
7. Xiong Y, Dowdy SC, Gonzalez Bosquet J, Zhao Y, Eberhardt NL, Podratz KC, Jiang SW. Epigenetic-mediated upregulation of progesterone receptor B gene in endometrial cancer cell lines. *Gynecol Oncol.* 2005; 99(1):135-41.
8. Moynihan AT, Hehir MP, Sharkey AM, Robson SC, Europe-Finner GN, Morrison JJ. Histone deacetylase inhibitors and a functional potent inhibitory effect on human uterine contractility. *Am J Obstet Gynecol.* 2008;199(2):167.e1-167.e7.
9. Tyson-Capper AJ, Cork DM, Wesley E, Shiells EA, Loughney AD. Characterization of cellular retinoid-binding proteins in human myometrium during pregnancy. *Mol Hum Reprod.* 2006;12(11):695-701.
10. Madsen G, Zakar T, Ku CY, Sanborn BM, Smith R, Mesiano S. Prostaglandins differentially modulate progesterone receptor-A and -B expression in human myometrial cells: evidence for prostaglandin-induced functional progesterone withdrawal. *J Clin Endocrinol Metab.* 2004; 89(2):1010-3.



*The Specialist Obstetrician Locum Scheme is funded by the Australian Government.*

SOLS provides locums for Fellows and GP Obstetricians in rural Australia.

Further information can be obtained from the SOLS website:

[www.ranzcog.edu.au/sols/index.shtml](http://www.ranzcog.edu.au/sols/index.shtml)

#### **SOLS Project Coordinators:**

tel: +61 3 9412 2912

fax: +61 3 9415 9306

[sols@ranzcog.edu.au](mailto:sols@ranzcog.edu.au)