

## Relaxin and Preterm Birth

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### Summary

Preterm birth (PTB) is a global problem with a high incidence in the developing world. Relaxin (RLN) has classically been associated with parturition, but its role(s) in the human have been difficult to determine. For the first time, we bring together the systemic (ovarian) and auto-crine/paracrine (intrauterine) sources of RLN, in an attempt to understand how RLN contributes to PTB in women.

### Key words

Relaxin, preterm birth, systemic, autocrine/paracrine

The first global report on PTB uses data from 184 countries and more than 400 member organizations (Howson et al., 2012). If these babies survive, they often have lasting disabilities and as adults have an increased risk of major diseases. PTB is a complex multifactorial disease. There are two main sources of RLN in human pregnancy, the ovary (corpus luteum) and within the uterus, the decidua and placenta. The ovarian RLN enters the systemic circulation, targets the decidua/placenta via the blood, whereas decidual/placental RLN has only autocrine/paracrine actions, as shown in patients with ovum donation pregnancies, who have undetectable circulating RLN. Women destined to deliver preterm, have higher RLN levels in the second and third trimesters (Vogel et al., 2006). Indeed, elevation of circulating RLN has long been associated with PTB, for which there has been no explanation. In the choriodecidua, there is increased RLN gene expression in women with PPROM. Expression of the RLN receptor gene (RXFP1) is also increased in patients delivering at preterm (Bryant-Greenwood et al., 2007).

In normal gestation, RLN in the circulation and intrauterine production are both low. We have shown that RLN can modulate the proinflammatory cytokines secreted from the decidual macrophages at the maternal-fetal interface. Low RLN levels, as in normal pregnancy were anti-inflammatory, but high levels were proinflammatory (Horton et al., 2011). If the RLN levels were sufficiently high, the avascular chorion could then also be a target and indeed, *in vitro* these cells show only a proinflammatory response (Bryant-Greenwood et al, 2009).

Intrauterine infection is a major cause of PTB, it was important to know whether this affected RLN. Thus, intra-amniotic infusion of lipopolysaccharide (LPS) in monkeys and its incubation with human fetal membrane explants showed increased IL-6, but had no

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effect on RLN. On the other hand, because a proinflammatory intrauterine response is associated with PTB even in the absence of infection, we proposed that RLN alone may induce a local “sterile” inflammatory response. Using RLN treatment of human chorion cells and its intra-amniotic infusion in monkeys, IL-6 and IL-8 secretion were stimulated (Bryant-Greenwood et al., 2009). Therefore, although infection does not affect RLN, RLN alone is capable of producing a localized inflammatory response. However, elevated RLN can also augment the inflammatory response caused by a low level of intrauterine inflammation/infection (Horton et al., 2012). Thus, both ovarian and intrauterine RLN contribute to the pathophysiology of PTB.

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## References

- Bryant-Greenwood G.D., Kern A., Yamamoto SY., Sadowsky DW, Novy MJ. (2007) Relaxin and the human fetal membranes. *Repro Sci* 14: 8(suppl.) 42-45.
- Bryant-Greenwood GD., Yamamoto SY., Sadowsky DW., Gravett MG., Novy MJ. (2009) Relaxin stimulates interleukin-6 and interleukin-8 secretion from the extraplacental chorionic cytotrophoblast. *Placenta* 30: 599-606.
- Horton JS., Yamamoto SY., Bryant-Greenwood GD. (2011) Relaxin modulates proinflammatory cytokine secretion from human decidual macrophages. *Biol Reprod* 85: 788-797.
- Horton JS., Yamamoto SY., Bryant-Greenwood GD. (2012) Relaxin augments the inflammatory IL6 response in the choriodecidua. *Placenta* 33: 399-407.
- Howson CP., Kinney MV., Lawn JE. (2012) *Born too Soon: The Global Action Report on Preterm Birth*. World Health Organization, Geneva.
- Vogel I., Thorsen P., Hundborg H., Uldbjerg N. (2006) Prediction of preterm delivery using changes in serum relaxin in low risk pregnancies. *Europ J Ob Gyn Repro Biol* 128: 113-118.