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The basics of progestogens and estrogens

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Since early seventies it was shown that luteal phase deficiency, a cause of infertility and early pregnancy loss caused by inadequate secretory transformation of the endometrium resulted from deficient endogenous production of progesterone (P4). P4 is mandatory for early implantation, pregnancy maintenance, prevention of early or late miscarriage but also for prevention of preterm birth. It is shown that P4 modulates maternal immune response, suppresses inflammatory response, promotes myometrial relaxation and improves utero-placental circulation during pregnancy. However, it is not clear how a shift in the E/P4 ratio is achieved and how estrogen and progesterone signaling interacts at the level of the cervical cells before the onset of labor. In fact, the decrease of P4 activity before the onset of labor may become possible through the occurrence of modified isoforms PRB & PRA, modifications of the adjustment of the P4 receptor through transcription factors or through the non-genomic effect of P4. P4 induces a stimulation of NOS1 and inhibits the formation of gap junctions. P4 and its metabolites induce uterine quiescence through interactions between nuclear and membrane P4 receptors. P4 and its metabolites has also non-genomic relaxing effects on uterine contractility linked to the blockage of calcium influx and interact with some membrane receptors (GABAA and oxytocin receptors). Oral administered P4 undergoes several successive metabolism steps in the gut (5b-reductase activity), in the intestinal wall (5a-reductase activity) and in the liver (reductase and hydroxylase activities). 5?-pregnanolone and 5ß-pregnanolone bind GABAA receptor. Neuroprotective effects of progesterone and allopregnanolone have been demonstrated in many injury models, including cerebral ischemic stroke but also in neonates. The observation that Progesterone Receptor (PR) play a key role in the viability of neurons after ischemic stroke and in the remyelination of axons after a demyelinating lesion (with potential significant therapeutic implications) challenges the concept that the neuroprotective and regenerative effects of progesterone in the brain may be mainly mediated by allopregnanolone. Human studies suggest that the placenta contributes also directly and indirectly to allopregnanolone found in the circulation and potentially the foetal brain being able to modulate neuroendocrine responses to stress.

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