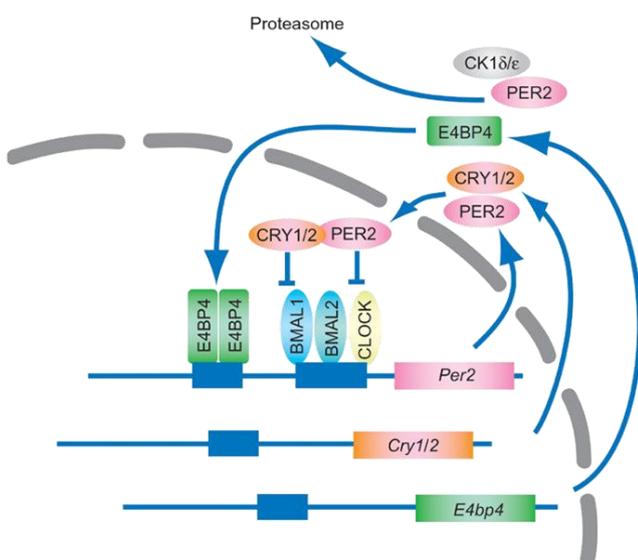


Clock genes in pregnancy

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Our journey on Earth begins from the moment of conception, however one of the most demanding physiological change we go through is passing from the intrauterine life to the extra-uterine one. It is still unknown the key process that starts the labor at that specific moment, the moment when the birth process begins. It seems, that in our hunt for the right answer we should start looking beyond our genes. Perhaps destiny seems to be alive in our genes, even if we don't believe it. From the discovered 21.000 genes, there are 5 genes that can play this role, among the other functions. And they are the so-called "clock genes". Now going back the connection line between clock genes and pregnancy starts in 2004, when Miler et al. suggested a role concerning circadian clocks in the parturition event. [3] Clock genes represent the basis of the circadian rhythmicity. The term "circadian" comes from the latin "circa diem" or "about a day," meaning these clocks can only keep time approximately, so it must be re-adjusted every day, therefore it depends on the time and strength of the light one is exposed. Pregnancy is arguably the most physiologically challenging state that an organism encounters across the life cycle. Still it's the most happy 9 month period in a women's life. During gestation, the conceptus follows a complex and dynamic program by which it is simultaneously fit to develop and live in a circadian environment provided by its mother and to prepare for the very different environment that it will experience after birth. There is evidence that the maternal rhythm of melatonin is one of the time signals to the fetus. [1] Melatonin hormone can cross unaltered the placenta and the blood-brain barrier, so the fetus will be exposed to the maternal circadian rhythm, which is mainly influenced by the light. [4] However there are important differences between the maternal and fetal circadian systems; for instance, the suprachiasmatic nucleus (SCN) is the master clock in the mother but not in the fetus. Despite this, several tissues/organs display circadian oscillations in the fetus. Physiological rhythms entrained by the circadian clock are present in virtually all organs including those of the reproductive system [8]

These clock genes are expressed mainly in the "master clock" of our body, in the SCN, nevertheless they express in almost every tissue. So they are expressed in the ovary, oviduct, and uterus too. In 2010 Nakamura et al suggested that ovarian steroid levels during the estrous cycle have a modulating influence of clock gene expression in the uterus.



At the cell level, interlocking transcription-translation feedback loops comprised of a core set of genes that include transcriptional activators and repressors: Bmal-1(Brain and muscle ARNT-like protein 1), Clock(Circadian locomotor output cycles kaput), Per1-2-3(Period), and Cry1-2(Cryptochrome), and their protein products results in circadian oscillation. The oscillating expression levels of genes comprising the molecular clock are responsible for the generation of circadian rhythmicity. [1, 2] The current molecular model for the generation of circadian oscillations is based on interlocked negative feedback loops in gene expression. Once PER and CRY proteins accumulate, they form nuclear complexes that interfere with BMAL1/CLOCK mediated transactivation, and therefore inhibit their own transcription. This negative feedback loop generates cycles of around 24h in gene expression. The PER and CRY repressors are

subjected to posttranslational modification and degradation. In addition, posttranslational events such as the further control of protein phosphorylation, sumoylation, acetylation, O-GlcNAcylation, degradation, and nuclear entry, contribute critically to the generation of daily oscillations in clock gene products. ^[5] The secondary autoregulatory feedback loop includes Rev-erb α , which is a direct target of the CLOCK -BMAL1 transcription activator complex. ^[11] It has also been described that these genes empower other functions like male and female fertility, hair growth, joint and ligament ossification. Then again there may be also a connection between the beginnings of the labor and deliver at a certain time of the day, which may be linked to clock genes. It has also been described an upregulation in expression of these genes near the time of parturition in the placenta.

In a study on rats it was described, that pregnancy alters the expression and circadian variation of clock genes in maternal liver, possibly contributing to maternal physiological adaptations. This study also demonstrates several pregnancy-induced changes in clock gene expression. ^[6] Another pregnancy related pathology, preeclampsia is a major public health issue, associated with a significant maternal and fetal morbidity and mortality worldwide. The disruption of the light/dark cycle (chronodisruption) in pregnancy has been associated with adverse outcomes. Slightly increased risk for "small for gestational age" babies, "low birth weight" babies, preterm deliveries, miscarriage has been reported in shift working women. Importantly, disturbances in clock gene expression are implicated in a range of pathologies including cancer and obesity. Circadian variation may be an important component of the normal placental phenotype.

A clear linkage to uterine physiology and clock genes expression is awaiting to be found. As the science is advancing, there is more evidence that our DNA is hiding so much more that we've ever imagined. But for right now, enlightening these developments, it will greatly contribute to new diagnostic and therapeutic approaches in obstetrics and gynecology.

Bibliography

1. Seron-Ferre M et al. -Circadian clocks during embryonic and fetal development (2007)
2. Christine K. Ratajczak et al. - Clock Gene Expression in Pregnancy-Related Tissues During Late Gestation in the mouse (2009)
3. James Olcese et al. - Circadian clocks and pregnancy (2013)
4. María Serón-Ferré et al. - Circadian rhythms in the fetus (2012)
5. Agnès J. Ditisheim et al. - Biological Rhythms and Preeclampsia (2013)
6. Michaela D. Wharfe et al. - Circadian Variation in Placental and Hepatic Clock Genes in Rat Pregnancy (2011)
7. Akiyama S et al. - The uterus sustains stable biological clock during pregnancy. (2010)
8. B.J. Waddell et al. - A rhythmic placenta? Circadian variation, clock genes and placental function (2012)
9. Kennaway DJ et al. - Circadian rhythms and fertility. (2012)
10. Mendez N et al. - Timed maternal melatonin treatment reverses circadian disruption of the fetal adrenal clock imposed by exposure to constant light. (2012)
11. C.H. Ko et al. - Molecular and Genetic Bases for the Circadian System (2013)