Nature Reviews Endocrinology | Published online 12 Feb 2016; doi:10.1038/nrendo.2016.21

ImageSource

ENDOCRINE DISRUPTORS

Reproductive consequences of analgesic use during pregnancy

> "analgesic use during pregnancy could have implications for the fertility of resulting daughters and granddaughters"

Endocrine-disrupting chemicals (EDCs) have the potential to adversely affect development (reproductive or otherwise) of the growing fetus and subsequent fertility and health in offspring. If fetal germ cells (FGCs) are affected, these effects could be transmitted to the next generation.

The possibility that analgesics, which are widely used by pregnant women, might adversely affect fetal development is of growing interest. A new study published in *Scientific Reports* adds to these concerns. The study, conducted in pregnant rats, shows that *in utero* exposure to the analgesics paracetamol (acetaminophen) or indomethacin affects the number and development of FGCs, which is associated with negative fertility attributes in first generation (F1) female offspring. As some abnormal ovarian effects were also evident in F2 female offspring, the findings, if translatable to humans, suggest that analgesic use during pregnancy could have implications for the fertility of resulting daughters and granddaughters.

As paracetamol and indomethacin are inhibitors of cyclooxygenase 2 (COX2; an enzyme involved in prostaglandin synthesis), the researchers first sought to determine whether FGCs and somatic cells of male and female rats expressed COX2 and prostaglandin receptors. Pregnant rats were administered either indomethacin by gavage (at a daily dose of 0.8 mg/kg) during the masculinization programming window (from embryonic day (e) 15.5 to e18.5) or paracetamol subcutaneously (at a daily dose of 350 mg/kg) from e13.5 to e21.5. Both male and female fetal gonads expressed COX2; furthermore, FGCs expressed prostaglandin receptors such as prostaglandin E2 receptor EP2 subtype (commonly known as EP2). The findings confirmed that FGCs and somatic cells are both sources of, and targets for, prostaglandins in the rat, and suggested that analgesic use could alter physiological processes regulated by prostaglandins in FGCs.

The researchers next investigated whether exposure of pregnant rats to either paracetamol or indomethacin altered FGC development and reproductive function in F1 offspring or the F2 generation. Analgesic exposure reduced F1 FGC numbers in both male and female rats and altered the timing of FGC development in a sex-dependent manner; meiotic entry in oogonia was delayed in F1 female rats, whereas FGC differentiation was hastened in F1 male rats. The effects persisted into adulthood in F1 female rats, which had smaller ovaries and litters than control rats. Conversely, F1 male rats had normal germ-cell numbers and fertility. Mating of male and female adult F1 rats with controls produced female offspring (F2) with reduced ovarian size; F2 male rats had normal reproductive development. As the effects on F2 female rats were transmitted via both male and female parents, the findings suggest that an epigenetic mechanism underlies transmission of the effect from the germ line to F2 female rats.

"Assuming that the same mechanisms and effects translate to humans, we do not have any clear information on how long the human fetus would need to be exposed to painkillers, at what dose, and when during gestation, for comparable effects such as reduced oocyte number to occur," explains lead investigator Richard M. Sharpe. "For the moment, all our results do is reinforce current UK National Health Service (NHS) advice to pregnant women on the use of painkillers during pregnancy." Michael K. Skinner of Washington State University in Pullman, Washington, USA, who was not involved in the study comments: "this is the first observation that this class of therapeutics promotes intergenerational effects." He adds, "these therapeutics, which are commonly used during pregnancy, need to be further investigated to assess their generational impact on offspring and subsequent generations."

David Holmes

ORIGINAL ARTICLE Dean, A. *et al.* Analgesic exposure in pregnant rats affects fetal germ cell development with inter-generational reproductive consequences. *Sci. Rep.* **6**, 19789 (2016)

FURTHER READING. Jégou, B. Reproductive endocrinology: Paracetamol-induced endocrine disruption in human fetal testes. *Nat. Rev. Endocrinol.* **11**, 453–454 (2015) | NHS. *Can I take paracetamol when I'm pregnant?* [online], http://www.nhs.uk/chq/Pages/2397.aspx?CategoryID=54& (2015)