Mild painkillers in pregnancy associated with increased risk of male reproductive problems

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New evidence has emerged that the use of mild painkillers such as paracetamol, aspirin and ibuprofen, may be part of the reason for the increase in male reproductive disorders in recent decades. Research published in Europe's leading reproductive medicine journal *Human Reproduction* today (Monday 8 November) shows that women who took a combination of more than one mild analgesic during pregnancy, or who took the painkillers during the second trimester of pregnancy, had an increased risk of giving birth to sons with undescended testicles (cryptorchidism) – a condition that is known to be a risk factor for poor semen quality and testicular germ cell cancer in later life.

The researchers from Denmark, Finland and France found that women who used more than one painkiller simultaneously (e.g. paracetamol and ibuprofen) had a seven-fold increased risk of giving birth to sons with some form of cryptorchidism compared to women who took nothing.

The second trimester appeared to a particularly sensitive time. Any analgesic use at this point in the pregnancy more than doubled the risk of cryptorchidism. Of the individual painkillers, ibuprofen and aspirin approximately quadrupled the risk of cryptorchidism, while a doubling of the risk (although non-statistically significant) was found for paracetamol. Simultaneous use of more than one painkiller during this time increased the risk 16-fold.

These findings were supported by work that the researchers Dr Ulla Hass at the Technical University of Denmark (Søborg, Denmark) and Dr

Bernard Jégou from INSERM (Institut National de la Santé at de la Recherche Médicale) at the University of Rennes (Rennes, France) carried out in rats. They found that analgesics disrupted androgen production, leading to insufficient supplies of the male hormone testosterone during the crucial early period of gestation when the male organs were forming. The effects of the analgesics on the rats was comparable to that caused by similar doses of known endocrine (hormone) disrupters such as phthalates – a family of chemical compounds used in the manufacture of plastics such as PVC.

Dr Henrik Leffers, senior scientist at the Rigshospitalet in Copenhagen (Denmark), who led the research, said: "If exposure to endocrine disruptors is the mechanism behind the increasing reproductive problems among young men in the Western World, this research suggests that particular attention should be paid to the use of mild analgesics during pregnancy, as this could be a major reason for the problems."

The study looked at two groups of women, 834 in Denmark and 1463 in Finland, who joined the study while they were pregnant. In Finland the women answered written questionnaires about their use of medication during pregnancy and in Denmark the women did the same or took part in a telephone interview, or both. The telephone interview asked specifically about the use of painkillers during pregnancy, while the written questionnaires did not. The baby boys were examined at birth for any signs of cryptorchidism, ranging from a mild form of the condition, in which the testis is located high in the scrotum, to the more severe form, in which the testis is so high up in the abdomen that it is non-palpable.

The researchers found that women significantly under-reported the use of painkillers in the written questionnaire because they did not consider mild painkillers to be "medication". Among the 298 Danish mothers who took part in both the self-administered questionnaire and the telephone

interview, 30.9% reported using painkillers in the questionnaire, but 57.2% reported it in the telephone interview.

The researchers could find no statistically significant effect in the group of Finnish women, but found significant effects amongst the Danish women.

Dr Leffers said: "We do not quite understand why the Finnish cohort does not show the same associations as the Danish cohort. However, the use of mild analgesics in the Finnish cohort was only examined by questionnaires, not by telephone interviews, and the telephone interviews gave the most reliable information in the Danish cohort, which may explain some of the differences. Moreover, the prevalence of cryptorchidism is much lower in Finland (2.4%) compared to Denmark (9.3%) and, therefore, this would require a larger cohort to find the same number of cases."

The work examining the effects of the analgesics in rats showed that intrauterine exposure to paracetamol reduced the anogenital distance (the distance between the anus and the genitals) in the offspring. AGD is a sensitive marker for reduced intrauterine androgen levels and effects on AGD predicts increased risk for impaired reproductive performance of the adult animal. The researchers also found that mild analgesics reduced levels of testosterone in the rat foetal testis by approximately 50%.

Dr Jégou said that the mechanism by which mild analgesics reduced testosterone was poorly understood. "It seems to be related to their mode of action which involves inhibiting the production of prostaglandins – locally acting messenger molecules. In another study by David Kristensen et al., we have shown that endocrine disruptors of the phthalate type are almost as potent inhibitors of prostaglandin synthesis as pharmaceutical inhibitors such as mild analgesics. However, currently

we do not know how a reduction of prostaglandin synthesis can reduce testosterone production."

The researchers say that there has been a marked increase in the incidence of congenital cryptorchidism in recent decades, notably in Denmark where it has increased from 1.8% in 1959-1961 to 8.5% in 1997-2001. "The magnitude of this difference is too large to be accounted for by random fluctuations and differences in ascertainment. Moreover, this finding is in accordance with the reported decline in reproductive health in the adult male population over the past five decades," they write in their paper.

Dr Leffers said: "Although we should be cautious about any over-extrapolation or over-statement, the use of mild analgesics constitutes by far the largest exposure to endocrine disruptors among pregnant women, and use of these compounds is, at present, the best suggestion for an exposure that can affect a large proportion of the human population."

The researchers say that the risk from the analgesics is markedly higher than that seen for known endocrine disrupters such as phthalates, and that, as most Western women are inevitably exposed to low levels of endocrine disrupters, these together with analgesic use, could be contributing to the increased incidence of cryptorchidism and later life reproductive problems.

Dr Leffers said: "A single paracetamol tablet (500 mg) contains more endocrine disruptor potency than the combined exposure to the ten most prevalent of the currently known environmental endocrine disruptors during the whole pregnancy. In fact, a single tablet will, for most women, be at least a doubling of the exposure to the known endocrine disruptors during the pregnancy and that dose comes on a single day, not spread out over nine months as with the environmental endocrine disruptors. Thus, for women using mild analgesics during the pregnancy, the mild

analgesics will be by far the largest exposure to endocrine disruptors."

The researchers say that more research is urgently needed, particularly epidemiological studies. They also recommend that advice to pregnant women on analgesic use should be reconsidered. "Women may want to try to reduce their analgesic use during pregnancy," said Dr Leffers. "However, as biologists this is not something we can advise women about. So we recommend that pregnant women seek advise from their physician before using mild analgesics and in general follow the advice to use as little medicine during pregnancy as possible."

More information: "Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat", by David M. Kristensen et al. Human Reproduction journal. doi:10.1093/humrep/deq323

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