

Egyptian Fertility Sterility Society

The 25th Editorial

Does paracetamol interfere with cell division and thereby disrupt pre-implantation embryonic development?

Prof. Ibrahim Mahrous, Al Azhar University

Dr. Mohamed El Sherbiny, MOH

What is Known Already?

Data from the last decades have shown that an estimated 10–40% of all embryos fail to implant, and an additional 10% of pregnancies are likely lost after implantation but before clinical recognition ([1-7]

Over-the-counter mild analgesic paracetamol (known as acetaminophen Panadol®) is the active pharmaceutical ingredient in more than 600 different medications used to relieve mild to moderate pain and reduce fever [8].

Paracetamol is widely used by women of reproductive age and during pregnancy, as it has been considered of minimal risk for use during pregnancy. [9]

The maximum single dose (oral or parenteral) 1000 mg and the maximum dose 4000 mg per 24 hours [10]

Although studies have shown that paracetamol exposure at non-cytotoxic levels inhibits cell proliferation, impairs DNA repair, and increases DNA fragmentation [11-15], up to 65% of pregnant women in the USA and an estimated 50% globally use paracetamol [16-20]. While these studies have yielded novel insights into abortion and preterm labor, they do not fully elucidate the risk of early embryonic loss within the first weeks of pregnancy.

What is New?

A recent study done at Denmark in 14 medical department by 26 authors encompassing human embryos and mouse pregnancy model. [21]

I. Human model: A total of 90 human embryos were exposed in vitro (22 cleavage stage and 68 blastocyst-stage embryos)

II. Mouse pregnancy model: Experiments were run in two independent cohorts of 24 females and 12 males. Upon arrival, females were housed in 12 boxes of two and males six-by-six.

This recent study reported that after exposure to paracetamol, it is found that:

1-A hindered cell cycle progression, likely by inhibiting ribonucleotide reductase, leading to reduced DNA synthesis and accumulation in the S-phase.

2- A decreased cell numbers in mouse and human cleavage-stage embryos or caused direct embryonic death

3- Similar exposure to mouse and human blastocyst-stage embryos resulted in a reduced inner cell mass and decreased DNA synthesis, respectively

Implications of This Findings:

The widely used mild analgesic paracetamol could contribute to early embryonic loss by impairing initial cell divisions. Thus paracetamol should be used with caution by women attempting to conceive (minimal dosage and duration when indicated with cold compress for hyperpyrexia or rest for pain).

References

- 1-Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med*;340:1796–1799. 1999
- 2-Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. *Fertil Steril*;65: 503–509. 1996
- 3- Wang X, Chen C, et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril*; 79:577–584. 2003
- 4- Jarvis GE. Estimating limits for natural human embryo mortality. *F1000Res* 2016a;5:2083.
- 5-Jarvis GE. Early embryo mortality in natural human reproduction: what the data say. *F1000Res* ;5:2765. 2016
- 6-Foo L, Johnson S, Marriott L .et al Peri-implantation urinary hormone monitoring distinguishes between types of first-trimester spontaneous pregnancy loss. *Paediatr Perinat Epidemiol*;34:495–503. 2020
- 7- Muter J, Lynch VJ, McCoy RC, Brosens JJ. Human embryo implantation. *Development*;150:dev201507. 2023

- 8- Bauer AZ, Swan SH, Kriebel D et al. Paracetamol use during pregnancy—a call for precautionary action. *Nat Rev Endocrinol*;17:757–766. 2021
- 9- FDA. Possible risks of pain medicine use during pregnancy. 20015.
- 10- Philip Thornton, DipPharm. Drug.Com March 7, 2025.
- 11-European Medicines Agency. PRAC recommendations on signals: adopted at March 2019
- 12- Hongslo JK, Bjørge C, Schwarze PE et al. Paracetamol inhibits replicative DNA synthesis and induces sister chromatid exchange and chromosomal aberrations by inhibition of ribonucleotide reductase. *Mutagenesis*; 5:475–480. 1990
- 13- Brunborg G, Holme JA, Hongslo JK. Inhibitory effects of paracetamol of DNA repair in mammalian cells. *Mutat Res*;342:157–170. 1995
- 14- Wiger R, Finstad HS, Hongslo JK, Haug K, Holme JA. Paracetamol inhibits cell cycling and induces apoptosis in HL-60 cells. *Pharmacol Toxicol*;81:285–293. 1997
- 15- Holm JB, Mazaud-Guittot S, Danneskiold-Samsøe NB, Chalmey C, Jensen B, Nørregård MM, et al. Intrauterine exposure to paracetamol and aniline impairs female reproductive development by reducing follicle reserves and fertility. *Toxicol Sci*;150:178–189. 2016
- 16- Smarr MM, Kannan K, Chen Z, Kim S, Buck Louis GM. Male urinary paracetamol and semen quality. *Andrology*;5:1082–1088. 2017
- 17- Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol*;193:771–777. 2005
- 18- Servey J, Chang J. Over-the-counter medications in pregnancy. *Am Fam Physician*;90:548–555. 2014
- 19- Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: a systematic review, meta-analysis, and meta-regression analysis of cohort studies. *Am J Epidemiol*;187:1817–1827. 2018
- 20- Bertoldi AD, Rifas-Shiman SL, Boing AC, Silva da Dal Pizzol T, Miranda VIA, Silveira MPT, Freitas Silveira M, Domingues MR, Santos IS, Bassani DG et al. Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood. *Paediatr Perinat Epidemiol*; 34:267–277. 2020
- 21- Brian S. Nielsen, Morten R. Petersen, Javier Martin-Gonzalez, Christian Holmberg, Heidi K. Mjoseng, Hanne Frederiksen Paracetamol (N-acetyl-para-aminophenol) disrupts early embryogenesis by cell cycle inhibition 1, Cristal Rosentha, Emma M. Jørgensen, Palle Serup, Sarah L. et al. Paracetamol (N-acetyl-para-aminophenol) disrupts early embryogenesis by cell cycle inhibition. *Human Reproduction*, , 00(00), 1–17. 2025