

Ibuprofen and its associated alterations in testicular physiologyHafsa Jawaid,¹ Afshan Hussain,² Nida Faisal³

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) most widely used for analgesic, anti-inflammatory and anti-pyretic indications.¹ It acts by inhibiting the activity of cyclooxygenases (COX1 and COX2), responsible for the synthesis and release of prostaglandins.² However, recent studies have found that ibuprofen can cause alterations in testicular physiology which may lead to disturbances in male sexual function and subsequent infertility.^{3,4}

Ibuprofen is considered extremely effective and is commonly used for self-medication practices, especially by pregnant women during early pregnancy with up to 28% reporting use despite its well-known property of placental transmission.³ However, it has been associated with risk of congenital anomalies of male reproductive tract such as cryptorchidism, shorter anogenital distance (AGD) and hypospadias reflecting subnormal levels of foetal and neonatal androgens upon drug consumption.³

Recent study of 2017, conducted in France, on human foetal testes concluded that ibuprofen exposure at 8-9 gestational weeks suppressed testosterone and anti-mullerian hormone (AMH) production along with a reduction in expression of several steroidogenic enzymes. Hence, it was established that ibuprofen consumption during the first trimester causes direct disturbances in foetal testicular function.³

Antiandrogen effects of ibuprofen in adult men were also documented through a clinical trial published in the Proceedings of the National Academy of Sciences USA. The study revealed that the subjects exhibited an increase in LH levels by 33% and a decrease in testosterone/LH ratio by 23% after 44 days of 600 mg ibuprofen administration. This showed a state of "compensated hypogonadism" that caused a downregulation of testosterone synthesis and

subsequent rise in pituitary hormones.⁴

This was further supported by series of ex vivo studies that showed a significant dose dependent inhibition of testosterone levels on direct exposure of adult testes explants to doses of 10^{-9} to 10^{-4} M ibuprofen. In-depth study of gene expression revealed that a mechanism of transcriptional repression occurred in Sertoli cells and Leydig cells suppressing their endocrine capabilities and causing down regulation of testicular steroidogenesis.⁴

An increased trend in infertility cases has been reported in literature with 10-15% young couples affected in total out of which 50% of cases were attributed to male factor problems.⁵ Moreover, since ibuprofen is a commonly prescribed analgesic, there is a concern that women unaware of their pregnancy might overuse the drug in the first trimester. Therefore, it is important that health care providers are aware of this side effect in order to create awareness regarding the overuse of ibuprofen among pregnant women and adult men and prescribe alternative analgesics especially in these groups of population.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Source: None to declare.

References

1. Wood DM, Monaghan J, Streete P, Jones AL, Dargan PI. Fatality after deliberate ingestion of sustained-release ibuprofen: a case report. *Crit Care* 2006; 10: R44.
2. Orlando BJ, Lucido MJ, Malkowski MG. The structure of ibuprofen bound to cyclooxygenase-2. *J StructBiol.* 2015; 189: 62-6.
3. Ben Maamar M, Lesne L, Hennig K, Desdoits-Lethimonier C, Kilcoyne KR, Coiffec I, et al. Ibuprofen results in alterations of human foetal testis development. *Sci Rep.* 2017; 7: 44184.
4. Kristensen DM, Desdoits-Lethimonier C, Mackey AL, Dalgaard MD, De Masi F, Munkbøl CH, et al. Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism. *Proc Natl Acad Sci USA.* 2018; 115: E715-24.
5. Guney AI, Javadova D, Kirac D, Ulucan K, Koc G, Ergec D, et al. Detection of Y chromosome microdeletions and mitochondrial DNA mutations in male infertility patients. *Genet Mol Res.* 2012; 11: 1039-48.

.....
^{1,2}Dow University of Health Sciences, ³Civil Hospital, Karachi.

Correspondence: Hafsa Jawaid. Email: hafsa.jawaid1995@gmail.com