Received: 17 October 2018 | Revised: 20 November 2018 | Accepted: 27 November 2018

DOI: 10.1111/and.13228

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INVITED REVIEW

WILEY ANDROLOGIA

Effect of ibuprofen on semen quality

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Abstract

Ibuprofen is a widely used analgesic/antipyretic medication belongs to the nonsteroidal anti-inflammatory class. Even though the influence of ibuprofen on semen quality has been investigated in various occasions, the comprehensive understanding and discussion of its impact on semen quality is still yet to be determined. In this work, we systematically review and reveal the effect of ibuprofen on semen quality, and thus on fertilising capability. To achieve this goal, we searched the main research databases (Scopus and PubMed) from 1 June 1986 through 13 October 2018 for English-language articles and abstracts using the keywords "ibuprofen" versus "semen" and "sperm". In addition, related published articles or abstracts were also discussed if relevant. Altogether, the main stream of research, from both in vitro and in vivo studies, presents an adverse effect of ibuprofen on different sperm parameters such as motility, viability, count and DNA integrity; however, such effect is not yet confirmed in humans. Mechanisms by which ibuprofen affects semen quality may be by reducing testosterone and prostaglandin synthesis, chelating zinc ions and inhibiting nitric oxide synthesis. However, further research studies, mainly clinical, are still of great importance to confirm the effects of ibuprofen on semen quality.

KEYWORDS
ibuprofen, prostaglandins, semen quality, spermatozoa, testosterone, zinc

1 | INTRODUCTION

Ibuprofen (isobutylphenyl propionic acid) is a drug from the nonsteroidal anti-inflammatory (NSAID) family (Figure 1). It is commonly used to relief pain, fever and inflammation (Munoz et al., 2018; Rainsford, 2009). Most of time, ibuprofen is used in common painful diseases/disorders such as rheumatoid arthritis (Yeomans et al., 2018), dental pain (Li et al., 2012), menstrual periods (Dawood & Khan-Dawood, 2007) and migraines (Rabbie, Derry, & Moore, 2013). Ibuprofen can be taken orally (bioavailability: 80%–100%) or intravenously; when taken orally, typically, its action begins in less than one hour (Atkinson et al., 2015; Black et al., 2002).

Similar to other NSAIDs, ibuprofen acts by inhibiting the formation of prostaglandins via reducing the activity of cyclooxygenase (Lanza et al., 1999). Compared to other NSAIDs, ibuprofen might induce weaker anti-inflammatory effects; however, it is effective as analgesic and antipyretic medication (Olive, 2006).

The safety of ibuprofen in humans has been studied in various occasions and over decades since first introduced in United States (1974). A 15-years careful surveillance of post-marketing data from both normal people and patients clearly indicates that ibuprofen has a safety profile, particularly when compared with other NSAIDs such as aspirin (Royer, Seckman, & Welshman, 1984). As a component of multimodal pain-management, an integrated safety analysis showed that intravenous ibuprofen can be safely given prior to surgery (Southworth, Woodward, Peng, & Rock, 2015). While, ibuprofen is not recommended in pregnancy, particularly in the later pregnancy, as it may be harmful to the embryo, (Nezvalova-Henriksen, Spigset, & Nordeng, 2013).

Even though, ibuprofen safety in humans has been reviewed in various occasions and over long-term periods, the post-marketing surveillance and the phase IV studies are still of great importance to investigate its unique adverse effects on particular diseased conditions. One such examples in this specific context is the effect

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of ibuprofen on semen quality, and hence on fertilising ability of males. Therefore, in this work, we intended to systematically address and summarise the effect of ibuprofen on semen quality, and hence to underscore the required future research directions in this setting, which ultimately will aid the targeted patients (i.e., with poor semen quality), the physicians, the pharmacists and the scientists in the field to exactly comprehend the effect of this drug on semen quality. To achieve this goal, we searched the main research databases (Scopus and PubMed) from 1 June 1986 through 13 October 2018 for English-language articles and abstracts using the keywords "ibuprofen" versus "semen" and "sperm". Additionally, references from related published articles or abstracts were also discussed, if relevant, to support the comprehensive understanding, and thereby the precise conclusion and future research priorities.

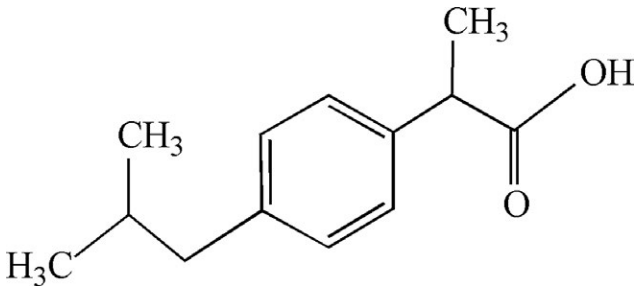

FIGURE 1 Chemical structure of ibuprofen

2 | EFFECT OF IBUPROFEN ON SPERM PARAMETERS

The main direct studies that investigate the effect of ibuprofen on sperm parameters (motility, count, viability, morphology, response to hypo-osmostic shock, acrosomal integrity and DNA integrity) and hence on sperm function were in vivo system studies (Table 1). Some other direct set of studies were in vitro studies. While up till now, very limited, and yet indirect, work in this context has been conducted on humans.

All direct in vivo system studies that investigate the effect of ibuprofen on sperm parameters were strictly conducted on adult male mice. While the in vitro studies utilised an ejaculated semen sample as illustrated in Table 1. In general, the in vivo system studies reveal a reduction in sperm count, motility, viability and DNA integrity upon exposure to ibuprofen for at least 35 days. Motility and viability of spermatozoa in vitro significantly decreased upon direct exposure (within minutes) to ibuprofen.

To the best of our knowledge, only one obvious human study, which is a retrospective cohort study, reveals the effect of ibuprofen on sperm parameters. As illustrated in this study, no alteration in the tested sperm parameters (motility, morphology, and count) was observed in assisted reproductive technologies (ART) patients who were on ibuprofen 3 months prior ART procedures. Accordingly, further clinical studies seem very important to reveal and confirm the effect of ibuprofen on human sperm function.

In fact, the observed effects of ibuprofen on sperm DNA damage are very serious and open the post-marketing surveillance studies of

TABLE 1 Studies conducted on ibuprofen and its direct reported effects on sperm parameters

Ibuprofen dose	Duration	Population	Effect	References
5.6 mg/kg/day	35 or 60 days	Adult male mice	(±) Motility (±) Viability (±) Acrosomal integrity (±) Response to hyposmotic shock	Stutz et al., (2000)
100 μg/ml	1 min	Washed spermatozoa (in vitro)	(–) Motility (–) Viability	Ingram, Zeller, Moss, and Hall (2006)
0.56, 1.12 or 1.68 mg/100 g/day	60 or 35 days	Adult male mice	(–) Motility	Martini et al., (2008)
30 mg/kg/day and 57 mg/kg/day	35 days	Adult male mice	(–) Motility (–) Morphology (–) Count (–) Sperm chromatin/DNA integrity	Roodbari et al., (2015)
15 mg/kg/day as part of APAP-ibuprofen combination)	2 times during sex determination period	Adult male mice	(–) Sperm count (19%) in utero-exposed (F0) adult males (–) Sperm motility (40%) in their offspring (F1) when both parents were exposed	Rossitto et al., (2018)
Therapeutic dose (~400 to ~1,200 mg/day)	3 months prior ART	ART patients	(±) Motility (±) Morphology (±) Count	Robinson et al., (2005)
92 ng/L	15, 30, and 45 min	Spermatozoa (in vitro)	(–) Sperm DNA integrity	Lucia Rocco et al., (2012)

Note. (–): decrease; (+): increase; (±): no change.

this drug, particularly on the healthiness of the offspring. It has been found that the use of ibuprofen by pregnant women in the second trimester is significantly correlated with low birthweight and presence of asthma in 1.5-year-old children (Nezvalova-Henriksen et al., 2013).

3 | MECHANISTIC STUDIES

3.1 | Effect of ibuprofen on gonadal function

The synthesis and regulation of testosterone is controlled by hypothalamic–pituitary–testicular axis (Roselli et al., 2016). Gonadotropin-releasing hormone is released by the hypothalamus gland in response to decreased levels of testosterone, which in turn induces the anterior pituitary gland to secrete luteinizing hormone and follicle-stimulating hormone (El-Migdadi, Banihani, & Banihani, 2005; Roselli et al., 2016). These hormones stimulate the production of testosterone from the testis, particularly from the Leydig cells (Zhang et al., 2018). At this stage, mechanistically, luteinizing hormone regulates the expression of 17β-hydroxysteroid dehydrogenase, which is crucial for testosterone synthesis (Wang, Zhang, & Gao, 2009; Zhou, Chen, Lin, Fei, & Ge, 2014). The produced testosterone activates certain genes in Sertoli cells in the testis, which ultimately enhances the differentiation of spermatogonia (Gonzalez-Herrera et al., 2006).

Ibuprofen has been found to decrease the production of testosterone (Kristensen et al., 2018; Stutz et al., 2000); However, the exact mechanism by which ibuprofen decreases human testosterone is not fully determined. It is demonstrated that ibuprofen may suppress testosterone production via suppressing the transcriptional repression in Leydig cells (Kristensen et al., 2018). In addition, ibuprofen was found to suppress testosterone in 8–9 GW foetal testes culture with concomitant decrease in expression of the steroidogenic enzymes (CYP11A1 gene, cholesterol side-chain cleavage enzyme; CYP17A1 gene, steroid 17α-monooxygenase; HSD17B3 gene, 17β-Hydroxysteroid dehydrogenase 3; INSL3 gene, insulin-like 3) (Ben Maamar et al., 2017). Accordingly, the disturbance in the production of steroidal hormones, particularly testosterone, as affected by ibuprofen could be behind the observed reduction in sperm count.

3.2 | Effect of ibuprofen on seminal prostaglandins

In males, prostaglandins, chemical compounds derived from the arachidonic acid and present in most bodily tissues, are produced mainly by seminal vesicle, and secondarily by prostate gland (Pourian, Kvist, Bjorndahl, & Oliw, 1995). Prostaglandins were found to play a major role in semen and sperm function. Primarily, they were found to increase progressive motility (grade a motility) of the spermatozoa and enhance its penetration into the ovum (Banihani, 2018; Gottlieb, Svanborg, Eneroth, & Bygdeman, 1988). Ibuprofen has been found to inhibit cyclooxygenase, also known as prostaglandin-endoperoxide synthase, by non-covalent binding, leading to a decrease in prostaglandins synthesis (Gierse, Koboldt, Walker, Seibert, & Isakson, 1999). The decreased synthesis of prostaglandins reduces the function spermatozoa, particularly the motility, and hence, its ability to achieve fertilisation. Therefore, it is obvious that the observed reduction in sperm parameters by the effect of ibuprofen, mainly motility, is attributable to decreased prostaglandins synthesis.

In fact, ibuprofen inhibits the activity of cyclooxygenase in two different ways based on the type of substrate presented (Prusakiewicz, Duggan, Rouzer, & Marnett, 2009). For example, when cyclooxygenase utilises arachidonic acid as substrate to synthesise prostaglandins, ibuprofen inhibits cyclooxygenase uncompetitively (Prusakiewicz et al., 2009). While ibuprofen inhibits cyclooxygenase competitively when 2-arachidonic acid is utilised as a substrate (Lanza et al., 1999; Roodbari, Abedi, & Talebi, 2015).

3.3 | Effect of ibuprofen on seminal zinc ions

Zinc ions are vital constituent of human semen (Foresta et al., 2014). Principally, they are secreted from prostate gland (Yoshida et al., 2008). Many scientists in the field have considered zinc as a marker of prostate function and seminal soluble components (Vivas-Acevedo, Lozano-Hernandez, & Camejo, 2011). For healthy males with normozoospermic semen, the level of zinc is approximately 135 ± 40 μg/ml (Canale et al., 1986).

Primarily, zinc ions in semen help to stabilize the DNA-containing chromatin in the spermatozoa (Canale et al., 1986). Studies have shown that zinc deficiency is correlated with lowered fertility as it increases sperm fragility and reduces sperm motility (Yuyan, Junqing, Wei, Weijin, & Ersheng, 2008). In addition, zinc deficiency was found to affect negatively spermatogenesis, leading to a reduction in sperm concentration (Dobrakowski et al., 2017; Madding, Jacob, Ramsay, & Sokol, 1986). It has been shown that ibuprofen can act as a bidentate chelator coordinatively bound to zinc ions via the deprotonated carboxylate group (Dendrinou-Samara et al., 1998). Such chemical property of ibuprofen can be correlated with its adverse effects on sperm parameters such as count, motility and viability.

3.4 | Effect of ibuprofen on nitric oxide production

Nitric oxide, also called nitrogen monoxide, is a free-radical signalling molecule gas produced in the body by nitric oxide synthase (NOS) from L-arginine and oxygen (Awasaki & Ito, 2016; Banihani, 2017). It is playing a vital role in many biological processes in the body, including vasodilation (Hall et al., 2014; Mees et al., 2007). Several studies have confirmed the presence of NOS (both endothelial, eNOS; and inducible, iNOS, isoforms) in human spermatozoa and that nitric oxide has a vital role in sperm function, particularly in maintaining adequate sperm motility (Banihani, Abu-Alhayjaa, Amarin, & Alzoubi, 2018; Herrero et al., 1994; Herrero & Gagnon, 2001). In fact, nitric oxide has been found to stimulate human sperm motility by activation of guanylate cyclase (sGC), subsequent formation of cyclic guanosine monophosphate and activation of cyclic-guanosine monophosphate-dependent protein kinases (Miraglia et al., 2011). NSAIDs, including ibuprofen, have been found to inhibit the expression of the iNOS gene, and hence nitric oxide production

(Aeberhard et al., 1995). In addition, ibuprofen has been found to reduce the activity of iNOS in glial cells (Stratman, Carter, & Sethy, 1997). Accordingly, the adverse effects of ibuprofen on sperm motility may be attributable, at least in part, to the reduction of NOS activity, and hence the amount of nitric oxide produced.

3.5 | Oxidative damage as affected by ibuprofen

The influence of ibuprofen on oxidative injury has been revealed in various species. Daphnia magna exposed to ibuprofen at 2.9 mg/L showed a significant increase in lipid peroxidation, and antioxidant enzyme (catalase and superoxide dismutase) activities after 12 hr, as well as increase in DNA damage after 48 hr exposures (Gomez-Olivan, Galar-Martinez, et al., 2014). In addition, a study conducted on C-carpio showed that ibuprofen at 17.6 mg/L for 12–96 hr significantly increased lipid peroxidation (Islas-Flores et al., 2014). Besides, the activity of the antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase was increased in blood, liver and gill of C-arpio to compensate the induced oxidative damage (Islas-Flores et al., 2014). Moreover, Zebra mussels Dreissena polymorpha exposed to ibuprofen at 1, 10 and 100 μg/L for 96 hr at 15°C had higher levels of oxidative damage and lipid catabolism (Andre & Gagne, 2017). Further, Corbicula fluminea exposed to ibuprofen (1, 5, 10, 15, 50 μg/L) for 21 days had significant increase in DNA damage and lipid peroxidation (Aguirre-Martinez, DelValls, & Laura Martin-Diaz, 2015). Furthermore, a significant increase in lipid peroxidation and protein carbonyl content as well as a change in catalase, superoxide dismutase and glutathione reductase activities with respect to the control group was induced by ibuprofen in Hyalella Azteca (Gomez-Olivan, Neri-Cruz, Galar-Martinez, Islas-Flores, & Garcia-Medina, 2014). This evidence indicates that ibuprofen induces oxidative damage, at least, in these tested species.

However, other studies have presented an antioxidant activity for ibuprofen. An in vitro study in 2009 showed that ibuprofen possesses a potential anti-radical scavenging activity as well as a metal chelating activity (Koncic, Rajic, Petric, & Zorc, 2009). In rats, ibuprofen was found to block the reduction of glutathione induced by rotenone injected intraperitoneally at 2.5 mg/kg for 10 days, and increase the basal concentrations of this drug in the striatum (Zaminelli et al., 2014). According to these researchers, such neuroprotective effects of ibuprofen may due to its antioxidant activity (Zaminelli et al., 2014). In addition, ibuprofen prevented the development of type 1 diabetic nephropathy in streptozotocin-induced diabetic rats (Liu et al., 2016). Such effect by ibuprofen appears to be attributable to its anti-inflammatory and antioxidant properties, mainly by activation of peroxisome proliferator-activated receptor γ (Liu et al., 2016). Moreover, ibuprofen protected rat livers from reactive oxygen species injury following tourniquet shock (Ward, Maldonado, Roa, Manriquez, & Vivaldi, 1995). Accordingly, this evidence excludes the suggestion that ibuprofen may affect negatively sperm parameters, at least in the in vivo systems, via oxidative injury.

This contradiction requires further studies to reveal the exact influence of ibuprofen on oxidative damage and lipid peroxidation. Considering the effect of ibuprofen on semen quality, studies that measure the effect of ibuprofen at different doses on testicular oxidative markers will be of great importance.

3.6 | Conclusions and future perspectives

In conclusion, the main stream of research studies (mainly in vivo system studies) demonstrates the presence of adverse effects of the use of ibuprofen, at different doses, on almost all sperm parameters such as motility, viability, count, morphology and DNA integrity. However, such effects are not yet established in humans due to the lack of research studies and research consensus. The adverse effects of ibuprofen on sperm parameters may be due to reduction in testosterone and prostaglandin synthesis, zinc-chelating activity of ibuprofen and inhibition of nitric oxide production.

While, collectively, further research studies, mainly clinical, are still of great importance to disclose the effects of ibuprofen on semen quality and sperm physiology, and hence on the ability of fertilisation. Our laboratory is now designing a long-term human research study to explore the effect of ibuprofen on sperm parameters, mainly sperm DNA damage.

ACKNOWLEDGEMENT

This study was supported by the deanship of research at Jordan University of Science and Technology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Banihani SA. Effect of ibuprofen on semen quality. *Andrologia*. 2019;e13228. https://doi.org/10.1111/and.13228