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The Detrimental Effects of Alcohol Consumption on Infertility of Humans and Laboratory Animals: A Review

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ABSTRACT

In recent decades, the decline in human fertility has become a major concern. However, unhealthy lifestyle practices, such as the use of addictive substances that contribute to infertility persist in society. Therefore, the current study reviewed the literature addressing the effects of alcohol consumption patterns on male and female fertility. Although alcohol intake is socially accepted, its detrimental influence on male and female fertility rates has been regularly observed in recent years. The findings have revealed that abstinence from chronic alcohol intake did not recover the testes from the negative effects of alcohol. Heavy drinking, defined as 8 or more glasses per week for a woman or 15 or more drinks per week for a man might impair female reproductive function. In conclusion, the implementation of an *in vivo* evidence strategy ranging from animal studies to preclinical ones has indicated that alcohol intake may be related to negative effects on reproductive parameters in both males and females. The present review deserves to be highlighted since it is significant for those who lead an unhealthy lifestyle, such as those who use alcohol.

Keywords: Addictive substances, Alcohol consumption, Reproductive function, Unhealthy lifestyles

INTRODUCTION

Historically, alcoholic beverages have played a significant role in the social lives of many people as they find moderate alcohol intake (1-2 glasses a day) enjoyable. Excessive alcohol use, on the other hand, could negatively affect health and enhance risks of some diseases (cardiovascular, cancer, and reproductive), criminality, accidents, and alcohol dependency. According to a report, the global death cases of alcohol consumption is 2.8 million per year among young people or those under the age of 70 (Ritchie and Roser, 2018).

Among the various issues related to alcohol consumption, it is worthwhile to pay more attention to the effects of alcohol consumption on the prevalence of infertility (Karjane et al., 2006; Pillai and McEleny, 2021; Rosielle et al., 2021). Based on the evidence, attempts to screen alcohol consumption support the alcohol-related complications that might arise, such as fetal alcohol spectrum disorders in women who are pregnant, intending to conceive, or are at risk of an accidental pregnancy (incidence of disability) (May et al., 2014). Alcohol in any form is not recommended for women, and it may have severe effects on the embryo after implantation (Smith, 1997; Bingham, 2015). Corollary, research on males has revealed that alcohol use might negatively affect sperm quality and testicular pathological markers (Stutz et al., 2004; Muthusami and Chinnaswamy, 2005; La Vignera et al., 2013).

Heavy drinking generally causes an increase in oxidative stress, chronic inflammation, and intestinal dysbiosis (Louevt and Mathurin, 2015; Widhiantara et al., 2021). Alcohol metabolism, on the other hand, produces a considerable number of reactive oxygen species (ROS) (Mackus et al., 2020). The formation of ROS in the liver after repeated alcohol intake leads to a decline in intracellular antioxidant defenses, such as superoxide dismutase, glutathione peroxidase, catalase, and heme oxygenase-1 that affects body homeostasis and induces apoptosis (Kurutas, 2015; Łuczaj et al., 2017). The disruption caused by excessive ROS build-up is of significant importance since various *in vivo* and clinical studies have indicated that it results in abnormal function of reproductive organs in both men and women (Steller et al., 2018).

More investigations, both experimental and clinical, are required to provide the most recent findings on the impact of alcohol use on the incidence of infertility. A recent case study indicated that azoospermia parameters had reverted to normal in patients after 3 months of not drinking alcohol (Finelli et al., 2021). As a result, to better understand the effect of alcohol intake on the incidence of infertility, this brief review aims to review the findings of the main preclinical and clinical studies on this issue.

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PRECLINICAL EVIDENCE

Pre-clinical evidence of reproductive disorders in male laboratory animals

Male mice and their offspring were studied to determine the impact of alcohol use on sperm count, motility, and structural alterations in the seminiferous tubules (Albadri, 2013). The physiological activity of sperm indicated a substantial decrease in the quantity and motility of sperm after 4 and 8 weeks of ethanol treatment in male mice, but not in their young offspring. Interestingly, the results of histological examination revealed that testicular lesions were developed in both parental male mice and adult male offspring. According to the findings of this study, alcoholism can cause damage to the testicular shape, sperm count, and motility in the parent and the subsequent progeny.

Exposure to pro-oxidants and toxic chemicals, such as aluminum, can enhance alcohol toxicity (Ghosh et al., 2021a). The microscopic structure of the testes was identified using a three-month-experimental study with 16 male rats, including three treatments and one control group. According to the study, there was a lack of normal spermatogenic cell distribution in the seminiferous tubules, and some spermatocytes were fragmented in the lumen. The use of combined treatment of ethanol and aluminum via the oral route caused vascular degenerative alterations in the cytoplasm of spermatogenic epithelium and Sertoli cells in testes (Ghosh et al., 2021a).

In another study, ethanol at a dosage of 3 gr (15%, v/v) per kg body weight was orally administered to adult male rats for 14 days (Jana et al., 2010). The expression of steroidogenesis and apoptosis was evaluated using Western blotting. The increased expression of steroidogenic acute regulatory proteins, 3-hydroxysteroid dehydrogenase (HSD), and 17-HSD levelled up the expression of active caspase-3, p53, Fas, and Fas-L resulting in an increase in the Bax/Bcl-2 ratio and translocation of cytochrome C from the mitochondria to the mitochondrial cytosol in the testes. There was also an increase in the transcriptional regulation of caspase-3, p53, Fas, Fas-L, caspase-3, and caspase-8 activity after repeated ethanol treatment. However, there was a decrease in the activity of 3-HSD, 17-HSD, and Glutathione peroxidase, as well as the activity of shared membrane potential mitochondria reactive oxygen species production and glutathione pool depletion in testicular tissue (Jana et al., 2010). Reactive oxygen species are involved in the inappropriate activation of the mitochondrial permeability transition, which leads to the alcohol-induced pro-apoptotic pathway (Hoek and Pastorino, 2002; Sastre, 2007). As a result, ethanol-induced germ cell death, necrosis, and cell proliferation suppression may all contribute to testicular degeneration (Zhu et al., 2000).

CYP2E1 is the only CYPE subfamily gene found on chromosome 10 and is highly expressed in numerous organs, including the liver and heart. The brain, nasal mucosa, renal cortex, testes, ovaries, and gastrointestinal system each have lower levels of expression (Arbitrio et al., 2021). In fact, the CYP2E1 gene is reported to play an important role in changing the metabolic process of numerous substances into hazardous metabolites, and the degree of toxicity increases when the production of this enzyme is stimulated by a specific exposure, such as alcohol (Liber, 1997).

Biomedical findings reported by Al-Bairuty et al. (2016) indicated that drinking alcohol at varying doses (20%, 30%, and 40%) for one month caused histological alterations in the testicular tissue and epididymis of albino male rats. This included basement membrane degradation, degeneration, necrosis, and a reduction in sperm count in the lumen of the seminiferous tubules. Moritiwon et al. (2021) also documented that traditional alcoholic drinks from Nigeria reduced the amount and quality of sperm, as evidenced by the spermatogenic characteristics of albino male rats. Another experiment was carried out to evaluate the effect of three brands of "Ghanaian herb-based alcoholic drink" (42% v/v) at dosages of 0.5, 2.5, and 5 mL/kg/day on the reproductive function of Sprague-Dawley rats during 21 days (Biney et al., 2020). The findings revealed that the three beverage brands may substantially lower sperm motility and serum testosterone while increasing overall antioxidant capacity. Overall, the researchers concluded that herb-based alcoholic beverages did not have a beneficial impact on the reproductive function of laboratory experimental animals and exhibited impaired sperm quality resulted from the antioxidant properties of the herbal ingredients (Biney et al., 2020).

There is also another research on traditional alcoholic beverages from various areas of Indonesia. "Tuak", a traditional Indonesian drink, has an alcohol level of up to 4% and is traditionally prepared by fermentation. The research addressing the effect of Tuak on the sperm quality of mice *(Mus musculus)* revealed that Tuak decreased spermatozoa quality (morphology and viability) and the process of spermatozoa production, and consequently, there was a decrease in the number of offspring produced (Tumengkol, 2015). Another alcoholic drink known as "Cap Tikus" has a 40% alcohol concentration and is made by distilling the liquid that originates from the "Enau" tree (Minahasa local language). The results indicated that drinking Cap Tikus substantially reduced the quality of spermatozoa, including concentration, motility, and morphology. This decline in quality could be also linked to the effects of alcohol, which may interfere with the functioning of the hypothalamus and anterior pituitary glands, both of which are crucial in the process of spermatogenesis (Melmambessy et al., 2015). Moreover, "Sopi", a traditional fermented drink from Maluku Province, Indonesia, is always drunk at different traditional local events. The findings revealed that the administration of Sopi drink to Sprague Dawley rats dramatically reduced the motility and quantity of spermatozoa (Wael and Mahulette, 2013).

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The practice of continually consuming alcoholic drinks has been extensively discussed, particularly its influence on the morphology and function of the testes. In contrast to the preceding assertion that recovery occurs following abstinence from alcohol intake, Dosumu et al. (2014) reported that abstinence after chronic alcohol consumption did not entirely reverse the deleterious effects of alcohol on the testes. This was demonstrated by the presence of testicular malondialdehyde, a low sperm count, motility, and a reduction in testicular diameter and the value of the cross-sectional area in the alcohol-free mice. On the other hand, testosterone levels rise and cause damage to the seminiferous epithelium, which may be the earliest signals of epithelial regeneration and recovery from alcoholism (Dosumu et al., 2014).

Pre-clinical evidence of reproductive disorders in female laboratory animals

Comparative experiments were conducted in rats (male, female, female ovariectomized) and young rats to assess the beneficial and detrimental effects of ethanol induction by administering various dosages (0; 0.5; 1.0; 2.0; and 2.5 g/kg/intraperitoneal) for 30 minutes. Overall, these results indicated that female rats were more susceptible to ethanol exposure due to an increase in ovarian hormone-mediated negative effects (Torres et al., 2014). The impaired reproductive function of female rats exposed to ethanol and aluminum for 3 months has been previously reported. The alcohol and aluminum exposure groups indicated ovarian damage and vacuolation, split of the zona pellucida, limited follicular development, decreased corpora lutea, and obstruction of blood arteries in the developing follicle (Ghosh et al., 2021b). Alcohol administration also inhibited the surge in proestrus Luteinizing hormone (LH) and ovulation in female rats. Furthermore, alcohol can gradually block the surge of LH-Releasing hormone (LHRH). Previous findings suggested that female rats fed alcohol can suppress gonadotropin surges largely by reducing LHRH production (Ogilvie and Rivier, 1997).

Pre-clinical evidence of reproductive disorders in human

Infertility is a public health issue characterized as the failure to achieve pregnancy after about 12 months of unprotected sexual intercourse (Huang et al., 2012). According to reports, the global incidence of infertility is 48.5 million, and the prevalence rate of infertility in all couples is considered to be between 12.5% and 24% (Slama et al., 2012; Mascarenhas et al., 2012; Datta et al., 2016). Alcohol consumption is one of the factors of infertility among couples. Alcohol can affect the control of the Hypothalamus-Pituitary-Adrenal (HPA) axis in males, causing a disturbance in the production of LH and Follicle-Stimulating Hormone (FSH).

Furthermore, even moderate alcohol intake in women might result in liver damage and menstrual cycle disruptions National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2011). Female infertility can be related to reduced or absent pituitary LH production (Walker and Tobler, 2021). Previous epidemiological findings by Wilsnack et al. (1984) showed that increased alcohol intake was associated with menstrual problems and infertility in as many as 917 women.

Various research has been carried out to better understand the effects of alcohol on reproductive health. However, there is still a dearth of medical evidence correlating drinking to an increased risk of infertility (Sharma et al., 2013). A meta-analysis of 57 research comprising 29914 individuals indicated a link between alcohol intake and sperm quality and quantity. In a study by Gaur et al. (2010), males who act as alcoholics had the lowest proportion of normozoospermic (12%), while 73% were categorized as heavy drinkers, 63% were moderate drinkers with teratozoospermia detected in sperm morphology, and as many as 64% were strong drinkers with oligospermia. Furthermore, drinking has been associated with an increase in oxidative stress and infertility (Ko et al., 2014). However, further study is required to demonstrate a relationship between oxidative stress and alcohol consumption and sperm quality, which is considered a sign of male fertility (Agarwal et al., 2014).

Heavy drinking, defined as 8 or more glasses per week for a woman or 15 or more drinks per week for a man, was associated with a decreased risk of fertility in both men and women (CDC, 2021; Mutsaerts et al., 2012), 50% less fertilization (Hakim et al., 1998), 50% lower rate of implantation (Rossi et al., 2011), increased risk of spontaneous abortion (Windham et al., 1997), fetal death (Bailey and Sokol, 2011), sporadic anovulation (Schliep et al., 2015), luteal phase dysfunction (Sinha, 2008; Lustyk et al., 2010), and abnormal blastocyst development (Gill, 2000). These different effects occur as a result of hormonal changes, such as increased estrogen levels, which can lower FSH levels and inhibit follicle development and ovulation (Rachdaoui and Sarkar, 2013). Nevertheless, many scientific studies are still unknown, particularly about the influence of alcohol on hormonal changes related to the reproductive system. However, Rachdaoui and Sarkar (2013) literature review has helped to synthesize the understanding of the influence of acute and chronic alcohol intake on hormonal variations in men and women (Table 1).

Several clinical investigations have also indicated that urine samples from healthy men who drink alcohol regularly have greater cortisol levels, which could directly affect spermatogenesis. The authors also reported that this was related to the HPA axis being inhibited in heavy drinkers (Thayer et al., 2006). Furthermore, since the hypothalamic-pituitary-gonadal (HPG) axis and its hormones play an important role in both male and female reproductive systems, its reduction has been related to alcoholism (Rachdaoui and Sarkar, 2013). The HPG dysfunction is also linked to low libido,

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infertility, and gonadal atrophy (Dabbous and Atkin, 2018). Alcohol-induced damage to the HPG axis, hypothalamus, pituitary, and gonads has been well-documented in recent studies resulting in decreased testosterone secretion in men and decreased progesterone in women (Rachdaoui and Sarkar, 2013; Finn, 2020; Finelli et al., 2021). Interestingly, HPG axis dysregulation affects not only reproductive failure but also other health issues, such as mood disorders, memory loss, osteoporosis, and muscular atrophy (Hackney, 2020).

The hormones estrogen, progesterone, and testosterone, for example, play a vital role in maintaining appropriate bone density and shape (Mohamad et al., 2016; Chidi-Ogbolu and Baar, 2019). Estrogen helps to relax blood arteries, lower the risk of atherosclerosis and cardiovascular disease in postmenopausal women (Iorga et al., 2017). Testosterone influences muscular growth and adiposity, as well as emotional and cognitive behavior in adult males (Widhiantara et al., 2021). The issue of alcoholism in pubertal humans is largely understudied. Several studies, however, have indicated that moderate alcohol intake can reduce adolescent females' estrogen levels for an extended period of time. Decreases in the hormones testosterone, LH, and FSH occur in pubertal males as a result of alcohol consumption (Diamond et al., 1986).

Table 1. Summary of hormonal changes induced by acute and chronic alcohol exposure in different animals

Endocrine	Hormone	Acute alcohol		Chronic alcohol		Animal Model	References
		Male	Female	Male	Female		
Hypothalamus	CRH	↑	↑	↔	↔	Macaque, Mice	(Barr et al, 2009; Sillaber et al, 2002)
	LHRH	↑	↑	↔	↔	Rats	(Sarkar and Fink, 1979)
	TRH	↔	↔	↓	↓	Rats	(Mason et al, 1988; Zoeller et al, 1996)
	GHRH	↓	↓	↓	↓	Rats	(Soszynski and Frohman, 1992)
	Somatostatin	↔	↔	↔	↔	Rats	(Soszynski and Frohman, 1992)
Anterior Pituitary Gland	ACTH	↑	↑	↓	↓	Rats	(Krishnan and Maickel, 1991)
	LH	↑	↑	↔	↓	Rats	(Ren et al., 2005a)
	FSH	↑	↑	↓	↑	Rats	(Ren et al., 2005b)
	TSH	↔	↔	↓	↓	Rats	(Mason et al., 1988; Zoeller et al., 1996)
	GH	↓	↓	↓	↓	Rats	(Sonntag and Boyd, 1988; Soszynski and Frohman, 1992)
	Prolactin	-	-	↑	↑	Macaque	(Mello et al., 1983)
Adrenal cortex	Cortisol	↑	↑	↑	↑	Rats	(Fahlke, 2000)
Testis	Testosterone	↓	↔	↓	↑	Rats	(Ren et al., 2005b)
Ovaries	Estrogen	↑	↑	↑	↑	Mice, Rats	(Imai et al., 2009; Hiney et al., 1998)
	Progesterone	-	↓	-	↓	Mice	(Imai et al., 2009)
Thyroid gland	T4	↔	↔	↓	↓	Rats	(Zoeller et al., 1996; Mason et al., 1988)
	T3	↔	↔	↓	↓		
Pancreas	Insulin	↓	↓	↓	↓	Mice	(Lang et al., 1998; Kim et al., 2010)

↑: Increased hormone release; ↓: Decreased hormone release; ↔: Unchanged hormone release (Source table adapted from Rachdaoui and Sarkar57). CRH: Corticotropin-releasing hormone, LHRH: Luteinizing hormone-releasing hormone, TRH: Thyrotropin-releasing hormone, GHRH: Growth hormone-releasing hormone, ACTH: Adrenocorticotropic hormone, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, TSH: Thyroid-stimulating hormone, GH: Growth hormone, T4: Thyroxine, T3: Triidothyronine.

CONCLUSION

Overall, the studies provided in this review have indicated that alcohol intake affects reproductive function parameters in both sexes of animals and humans. The effect of alcohol on males is frequently related to decreased sperm quality and quantity. Interestingly, heavy drinking, defined as 8 or more glasses per week for a woman or 15 or more drinks per week for a man can have a severe influence on pregnancy and other reproductive problems in females. The healing properties of post-alcohol abstinence should also be investigated further, as there are still several gaps in the findings of previous studies.

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DECLARATIONS

Authors' contribution

Made Nyandra, I Gede Widhiantara, and Putu Angga Wiradana designed and conceived the idea. Made Nyandra and I Gede Widhiantara collected the literature related to the paper idea. Putu Angga Wiradana wrote the manuscript and translated the manuscript into English. All authors read and approved the final manuscript.

Competing interests

The authors have not declared any conflict of interest.

Ethical consideration

Plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been checked by all the authors.

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