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Literature Review

Electronic Cigarettes on Sperm Quality: Review in Animal and Human Study

Teresita Marselina Nahak*[1], I Gusti Ngurah Pramesemara[1,2]

[1] Andrology Polyclinic at Kasih Ibu Hospital, Denpasar, Bali, Indonesia
[2] Department of Andrology and Sexology, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

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*) Corresponding author:
E-mail: tessanahak@gmail.com

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Abstract

Electronic cigarettes that are currently popular are used as nicotine replacement therapy. There are several substances contained in electronic cigarette liquid that have carcinogenic effects. These substances can also increase free radicals which in turn can cause oxidative stress. Nicotine, propylene glycol, and glycerol can cause disturbances in male reproductive function. Infertility can occur due to lifestyle factors, one of which is smoking. Nicotine found in cigarettes can reduce sperm quality, including concentration, mobility, viability, and sperm morphology. The purpose of this study was to determine the effect of electronic cigarettes on sperm quality. The research method uses a literature review system. The twelve studies that are in accordance with the topic of discussion are experimental studies on mice and rats, two studies on human, and one study on both human and rats. Five journals showed a significant decrease in sperm count and testosterone serum level, three other journals showed a significant decrease in sperm morphology and viability, six journals showed a decrease in sperm motility, seven journals showed a significant impairment of testis histological structure, four journals showed a decrease of steroidogenesis enzymes, and one journal showed a significant increase of DNA fragmentation due to the use of electronic cigarettes. Electronic cigarettes had an effect on sperm quality.

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1. Introduction

The use of electronic cigarettes (e-cigarette/vape) as a substitute for cigarettes is currently increasingly popular. By 2020, it is estimated that as many as 68 million people in the world will use electronic cigarettes[1] where the use of electronic cigarettes increases in adolescents and young adults aged 18 – 24 years.[2] Based on the Global Adult Tobacco Survey (GATS),[3] the prevalence of electronic cigarette users in Indonesia is 3% in 2021, this figure has increased tenfold compared to 2011, which was 0.3%.

In 2003, the electronic cigarette was created and patented by an engineer from China with several main objectives, namely (1) to reduce the mortality rate associated with the use of conventional cigarettes, (2) to help smokers to quit smoking, and (3) to reduce the cost of conventional cigarettes.[4] Electronic cigarettes are also used as nicotine replacement therapy, in which nicotine levels are reduced periodically with the supervision of a doctor.[5]

The liquid in electronic cigarettes contains chemical substances, including propylene glycol and glycerol which can produce vapor like conventional cigarette smoke with function as a carrier for nicotine; also, ethylene glycol, polyethylene glycol mixed with artificial flavors Some electronic cigarettes also contain nicotine.[4,6]

Based on research by the FDA, there are several substances contained in electronic cigarette liquid that have carcinogenic effects.[5] These substances can also increase free radicals which in turn can cause oxidative stress. [7] In addition, nicotine, propylene glycol, and glycerol can cause disorders of male reproductive function.[6]

Infertility is defined as a problem in the reproductive system, where there is failure to get pregnant after 12 months or more having sexual intercourse at least 2-3 times a week regularly without using contraception. Based on survey results in 2018, pregnancy failure in married couples for 12 months, 40% is caused by infertility in women, 40% is caused by men, 10% is caused by both, and 10% has no known cause.[8,9]

Infertility in men is divided into two categories, which are primary and secondary infertility. Primary infertility can be caused by infections, congenital abnormalities, malignancies, endocrine disorders, and immunological factors, whereas secondary infertility can occur due to age and lifestyle factors, one of which is smoking habits.[10] Nicotine found in cigarettes can reduce sperm quality, including concentration, mobility, viability, and sperm morphology.[11]

Based on research conducted by Holmboe et al (2020),[12] daily consumption of electronic cigarettes can cause a decrease in sperm count. The flavoring content in electronic cigarettes is also harmful to sperm quality, according to research at University College of London, electronic cigarette flavoring agents, especially chewing gum flavorings, can kill cells in the testes, while cinnamon flavoring has a negative impact on sperm motility.[13] Because of this discussion, researchers are interested in examining the effect of electronic cigarettes on sperm quality.

2. Review

The research method uses a literature review system with population in this study are articles and documents published in the last ten years, in Indonesian and English. Search data using the keywords Electronic Cigarettes, Sperm Quality, Infertility, Testis Histology, DNA Fragmentation, Lifestyle, Habit. Data searches were carried out on the Google Scholar, Pubmed, and Sciencedirect websites.

Fifteen continuous journals were obtained with the topic of discussion, with research designs on mice, rats, and humans. Based on the results of a review of the collected journals, it was found that there was an effect of electronic cigarettes on sperm quality.

In a 2019 study found a decrease in sperm count in treatment with exposure to electronic cigarettes containing nicotine, this can be caused by the nicotine content which when burned can produce free radicals which are toxic materials for the body. Free radicals are substances that normally exist in the body. However, if the production of free radicals or reactive oxygen (ROS) is higher than anti-free radicals (antioxidants), it will cause oxidative stress.[5]

According to the results of research conducted in Tunisia in 2016 and 2018, electronic cigarettes without nicotine content can reduce the number of testicular spermatozoa and epididymis of Wistar rats more than electronic cigarettes with nicotine. This is because there is one of the main ingredients in electronic cigarette liquid, namely propylene glycol, which when inhaled can cause disturbances in the reproductive system.[5] Propylene glycol can induce a decrease in the number of sperm cells and can also damage the sperm flagellum.[11]

In addition, there is another ingredient in the form of diacetin, which is an additive in the form of food flavors, where this substance can play a role

in cytotoxicity. These two studies also prove that electronic cigarettes without nicotine content can increase oxidative stress status. This research also examined the enzymes that play a role in the antioxidant system, which is increase in these enzymes indicates an increase in the production of free radicals or ROS which can cause a decrease in sperm count and damage to the process of spermatogenesis.[11,15]

A 2022 study in Indonesia reported a decrease in the diameter of the seminiferous tubules of mice exposed to electronic cigarette smoke with three different volumes of fluids. The number of sperm produced by the testes depends on the process of spermatogenesis that takes place in the seminiferous tubules, so that a decrease in the diameter of the seminiferous tubules is caused by a decrease in the number of sperm. The increase in free radicals produced by nicotine in electronic cigarettes can interfere with the process of spermatogenesis which in turn can have an impact on the diameter of the seminiferous tubules.[5,14]

Testosterone is the most active and dominant androgen hormone in maintaining the structure and function of the testes. Nicotine can inhibit testosterone biosynthesis in rat Leydig cells. Nicotine can also reduce testosterone and estradiol, as well as reduce sperm production and maturity.[15]

Free radicals originating from electronic cigarette liquid can increase the amount of lipid peroxidase, causing damage and decreasing the integrity of the spermatozoa membrane, which in turn will result in decreased sperm viability and quality.[15] This is in accordance with studies conducted by Goli et al, and Rahali et al that electronic cigarettes with or without nicotine can reduce the amount of plasma testosterone hormone and can reduce sperm viability. Research by Zulfikar et al in 2022 also supports that exposure to electronic cigarette smoke with more nicotine content per day will further reduce sperm viability.[7]

Similar study in 2022 reported that the more exposure to the content of electronic cigarettes, the sperm motility will decrease. An increase in reactive oxygen can affect energy production by mitochondria located in the middle, resulting in poor sperm motility (asthenozoospermia).[17] Reactive oxygen (ROS) which is a byproduct is released during cellular metabolism into semen.[24]

Cytokine levels in seminal plasma are associated with sperm quality parameters. ROS and cytokines have complex interactions, although ROS can promote cytokine expression and production, some cytokines can modulate prooxidants and antioxidants. In addition, spermatozoa membranes are rich in polyunsaturated fatty acids (PUFA), which makes spermatozoa susceptible to lipid peroxidation, and oxidative stress results in decreased sperm viability, and increased morphological defects in the middle part of the sperm, furthermore this dysfunction can cause a decrease in sperm motility.[24]

Another sperm quality studied was sperm morphology, based on research results in 2021, where electronic cigarettes with three different fluid volumes can increase abnormal sperm morphology. Increased reactive oxygen (ROS) is a cause of disruption of the normal shape of sperm. Phospholipids as a component that is abundant in the sperm plasma membrane, is the main target of ROS.

The result of the bond between fat and reactive oxygen produces lipid peroxidase, which produces a component, malondialdehyde (MDA), which is toxic and can damage the plasma membrane. If there is damage to the sperm membrane, cell metabolism will be disrupted which in turn will cause more and more abnormal forms of sperm.[7] Research in 2018, apart from getting results that electronic cigarettes can increase sperm abnormalities, there is also an increase in MDA levels as a marker of increased reactive oxygen.

DNA fragmentation, as a marker of damaged chromatin, has a role in male infertility.[25] DNA fragmentation can be caused by extrinsic factors, such as exposure to heat, smoking, or environmental pollution, also intrinsic factors, including failed apoptosis or oxidative stress.[26] Reactive oxygen plays a role in physiological processes and apoptosis, but if there is an excessive increase, it can cause bad effects, one of which is DNA fragmentation, but if the level of oxidative stress is not sufficient for cell apoptosis, it will disrupt sperm function, acrosomal exocytosis, and sperm-oocyte fusion.

Based on research conducted in South Korea, examining 84 men of reproductive age, an increase in DNA fragmentation was found in e-cigarette users.[23] This can happen because the nicotinic acetylcholine receptor in spermatozoa plays a role in changes in sperm parameters, acrosome reaction, mitochondrial function, apoptosis, chromatin and DNA integrity. Nicotine exposure can cause DNA damage in epigenetic reprogramming mechanisms, which in turn can impact the father's genetics and epigenetics on embryo development.[16]

There was also a relationship between exposure to electronic cigarettes and the induction of reactive oxygen in testicular or epididymal tissue. The nicotine contained in electronic cigarettes has anti- or pro-apoptotic effects on tissue. Based on research conducted in 2019 in Poland, exposure to electronic cigarette smoke can cause deformities in the shape and structure of the testicles and epididymis.[16]

In 2016 research proved that electronic cigarette fluid induction can disrupt the contents of the testicular seminiferous tubules and desquamation of germ cells. This can cause the formation of fragments in the seminiferous tubules and worsen sperm density.[15]

Steroidogenesis is the process of changing cholesterol into steroid hormones mediated by steroidogenic enzymes. Sex-steroid hormones produced by Leydig cells have a function in reproductive health and embryo development. Several enzymes that play a role in the steroidogenesis process are cytochrome P450scc (also known as CYP11A1, encoded by the CYP11A1 gene), and hydroxysteroid dehydrogenase (HSD) which are in the mitochondria and endoplasmic reticulum.[27]

According to research conducted in Italy, exposure to electronic cigarettes without nicotine content can reduce steroidogenesis enzymes, both cytochrome P450 and 3β hydroxysteroid dehydrogenase and 17β hydroxysteroid dehydrogenase. A similar study was also conducted in 2022 in Egypt, showing that exposure to electronic cigarettes for 4 weeks reduced the enzyme 17β hydroxysteroid dehydrogenase, but after stopping exposure for the next 4 weeks, there was an increase again, although not to normal.[17,18]

Electronic cigarettes have been promoted as a healthier alternative to tobacco cigarettes, and as a potential tool for smoking cessation.[28] Electronic cigarettes simulate the visual, sensory and behavioral aspects of smoking. Several studies suggest that sufficient levels of nicotine in electronic cigarettes can have physiological and behavioral effects.[29]

In research conducted in 2020, reporting 3 months of electronic cigarette use among motivated smokers, showed results in reducing tobacco cigarette consumption, when combined with low-intensity counseling.[29] This research supports the efficacy of e-cigarette use in the short term, leading to higher rates of cessation of tobacco cigarette consumption. All participants reported experiencing a significant reduction in consumption of conventional cigarettes per day, so the use of e-cigarettes allows smokers to achieve better results.[30]

In addition to electronic cigarettes, conventional cigarettes have a higher effect on sperm motility compared to electronic cigarettes. The cause that can occur is because electronic cigarettes do not contain tar or other toxic substances compared to conventional cigarettes so that the resulting oxidative stress will be lower.[14] However, both conventional cigarettes and electronic cigarettes can be dangerous because they both contain nicotine.[6]

Table 1. E-cigarette Effects on Sperm Quality

Method	Effects	References
15 Mice (Mus musculus), exposed to non-nicotine e-cigarette smoke and e-cigarette smoke with 18mg of nicotine.	Decrease Sperm Parameter: Sperm count	[5]
24 Mice (Mus musculus), exposed to e-cigarette smoke with a fluid volume of 1 mL, 2 mL, and 4 mL	Decrease Sperm Parameter: Sperm motility Sperm morphology	[7]
9 Wistar rats (Rattus norvegicus), exposed to conventional cigarette smoke and e-cigarette smoke.	Decrease Sperm Parameter: Sperm motility Sperm morphology	[6]
28 mice (Mus musculus), exposed to conventional cigarette smoke, given 1 cigarette/day, 2 cigarettes/day, 3 cigarettes/day; and e-cigarette smoke with a fluid volume of 0.7 ml/day, 1.3 ml/day, 2 ml/day.	Decrease Sperm Parameter: Sperm motility Sperm viability Decrease of seminiferous tubules diameter	[14]

24 Wistar rats (Rattus norvegicus), were given an IP injection of nicotine-free e-cigarette liquid and IP injection of e-cigarette liquid with 18 mg/ml nicotine in the testis.	Decrease Sperm Parameter: Sperm count Sperm viability Decrease in plasma testosterone level Increase in oxidative stress marker Malformation of testis histological structure Decrease of steroidogenesis enzymes	[15]
24 Wistar rats (Rattus norvegicus), were given an IP injection of nicotine-free e-cigarette liquid and IP injection of e-cigarette liquid with 18 mg/ml nicotine in the epididymis.	Decrease Sperm Parameter: Sperm motility Sperm viability Decrease in plasma testosterone level Increase in oxidative stress marker Malformation of epididymis histological structure	[11]
32 male mice, 16 mice were given aerosol and control e-cigarette for 5 weeks, 16 mice were given aerosol and control e-cigarette for 10 weeks.	Decrease Sperm Parameter: Sperm count Increase Sperm Parameter: Sperm count	[16]
30 male Wistar rats, 3 groups each given e-cigarettes 7.2 mg nicotine/day; conventional cigarettes nicotine 0.7 mg/stick; control group. The other 3 groups were observed for 2 weeks after administering each treatment.	Decrease Sperm Parameter: Sperm Morphology Malformation of testis and epididymis histological structure Apoptosis of spermatogonia and spermatocyte	[17]
30 rats, 3 groups; control group; the group was given e-cigarette 1ml/day for 5 days/week for 4 weeks; the group was given e-cigarette 1ml/day for 5 days/week for 4 weeks, then not exposed to anything for the next 4 weeks.	Decrease of serum testosterone level Increase in oxidative stress marker Malformation of testis histological structure Decrease of steroidogenesis enzymes	[18]
14 rats, 2 groups; control group, and the group was given a 3.5 volt, free nicotine electronic cigarette.	Increase in oxidative stress marker Impairment of testosterone biosynthesis enzymes	[19]

	Decrease of steroidogenesis enzymes	
20 mice, 2 groups; control group, and group exposed to electronic cigarette smoke.	Decrease Sperm Parameter: Sperm motility Increase in oxidative stress marker	[20]
40 male rats, 4 groups; negative control; positive control; administration of 15 and 30 puffs of electronic cigarette smoke.	Malformation of testis histological structure	[21]
Ejaculate from 30 men was cultured with 2 e-cigarette liquids containing each of cinnamon and bubblegum flavorings and containing propylene glycol. 6 mice, exposed to e-cigarette liquids containing each of cinnamon and bubblegum flavorings.	Decrease Sperm Parameter: Sperm concentration Sperm motility Apoptosis of testes	[22]
84 men of productive age, divided into 4 groups; non-smokers group; regular smokers' group; e-cigarette smokers' group; regular smokers/ e-cigarette smokers.	Increase in DNA fragmentation	[23]
Men 19 years old on average, divided into 5 groups; nonsmokers' group; e-cigarette smokers' group; cigarette smokers' group; snuff users group; marijuana users group.	Decrease Sperm Parameter: Sperm count Increase in total and free testosterone level	[12]

3. Summary

Electronic cigarettes with or without nicotine both in human and animal had influence the sperm parameters. The content of substances in electronic cigarette liquid can cause an increase in reactive oxygen which can cause a decrease in the number, viability, motility, normal morphology of sperm, and some other qualities of sperm e.g., increase DNA fragmentation, malformation of testis and epididymis histological structure. They also decrease the level of testosterone level and steroidogenesis enzymes.

This research is still far from perfect, it is hoped that in the future there will be more research on the effects of electronic cigarettes on sperm quality in humans.

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Author's Contribution

All authors have contributed to the final manuscript.

Conflict Of Interest

There are no conflicts of interest.

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