Amerta Nutrition
e-ISSN: 2580-1163 (Online)
p-ISSN: 2580-9776 (Print)
Putri and Nadhiroh | Amerta Nutrition Vol. 8 Issue 2 (June 2024). 318-327

LITERATURE REVIEW
English Version
OPEN ACCESS

A Literature Review: Association between Obesity and Infertility in Productive-Aged Men

Tinjauan Literatur: Hubungan Obesitas dan Infertilitas pada Pria Usia Produktif

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ARTICLE INFO

Received: *19-07-2023*
Accepted: *29-02-2024*
Published online: *07-06-2024*

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DOI:
10.20473/amnt.v8i2.2024.318-327

Available online at:
https://e-journal.unair.ac.id/AMNT

Keywords:
Obesity, Infertility, Sperm Quality, Sperm Quantity

ABSTRACT

Background: Obesity is a worldwide epidemic problem that is increasing continuously. Obesity negatively affects several functions in the body, including reproductive function (fertility). The prevalence of infertile couples in Indonesia in 2013 was 15-25% with male infertility accounting for 25-30% of total infertility cases.
Objectives: This study aimed to determine the association between obesity and infertility in productive-aged men.
Methods: The research results from eight observational studies gathered in accordance with inclusion criteria, credible literature on the topic of obesity and male infertility, were examined in this study using the literature review method. Additionally, the exclusion criteria encompassed references that were not accessible in full text and related to animal studies.
Discussion: Obesity can have a direct or indirect effect on male fertility through several mechanisms of hormonal profile changes. Moreover, the excessive conversion of androgens to estrogens caused by obesity can lead to an increase in aromatase activity and subsequent reproduction; this imbalance ultimately results in lower-quality sperm. Additionally, obesity causes high plasma leptin levels. Furthermore, sperm plasma membrane fluidity, impairing sperm motility, and increasing sperm deoxyribonucleic acid (DNA) damage are all negatively affected by leptin-induced increases in oxidative stress and the uncontrolled production of reactive oxygen species (ROS).
Conclusions: An increased BMI increases the risk of decreased sperm parameters, which indicates a higher level of infertility in men. Obese men may increase the risk of changes in sperm parameters both quantitatively (volume, number, and concentration) and qualitatively (motility, morphology, and sperm DNA).

INTRODUCTION

The prevalence of obesity, considered an epidemic problem, is continuously on the rise worldwide[1]. According to the World Health Organization (WHO), the terms overweight and obesity refer to abnormal or excessive accumulations of fat that have the potential to negatively affect health[2]. Moreover, a 2016 WHO report revealed that more than 1.9 billion adults aged 18 years and older are overweight, with more than 650 million of them being obese[2]. In Indonesia, the prevalence of obesity in adult men of productive age was 14.5%.[3]. In addition to contributing to various disorders, obesity increases the body's vulnerability to chronic diseases such as diabetes, cardiovascular disease, tumors or cancer, premature aging, and neurodegenerative diseases. Furthermore, obesity has a negative effect on several body functions, including reproductive function (fertility)[4]. However, the fact is that male infertility is both a contributing factor and a cause of infertility in almost 40% of couples who are diagnosed as infertile[5]. The causes of male infertility are multifactorial, with obesity potentially being the only major cause and a contributing factor in many cases. Semen parameter changes are hypothesized to be a result of obesity in men. Population-based epidemiologic evidence was not available until a decade ago. Based on previous research, obese men have nearly twice the risk of infertility[6]. It has been reported that obesity affects spermatogenesis as well as semen quality[7]. Obese men have increased adipose tissue, which raises leptin levels and triggers leptin resistance. Leptin resistance centers on the hypothalamus, where leptin is unable to stimulate the hypothalamic-pituitary-gonadal (HPG) axis[8]. Decreased activity of the HPG axis can inhibit the release of gonadotropin-releasing hormone (GnRH) in the hypothalamus, which in turn causes the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH is associated with the production of sertoli cells in seminiferous tubules, which serves to stimulate the formation of androgen-binding protein (ABP) and inhibin B. Meanwhile, inhibin B

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regulates the secretion and production of FSH by the pituitary gland. Inhibin B serves as feedback for GnRH to stop the release of FSH. Inhibin B also stimulates Leydig cells to synthesize testosterone[9]. Moreover, ABP plays a role in spermatogenesis. Decreased levels of LH are associated with a decrease in testosterone-related leydig cells in the formation of secondary genitalia such as Adam's apple, mustache, pubic hair, and others. These cells also support ABP in the process of spermatogenesis. Additionally, insulin resistance in obese men is induced by resistin, another adipose tissue hormone[10]. The function of testosterone to mediate normal spermatogenesis can be inhibited by the decreased levels of SHBG (*sex hormone binding globulin)* caused by increased insulin levels in obese men[11,12]. Hormonal changes can interfere with the process of spermatogenesis, resulting in a decrease in sperm quality or quantity. When testosterone levels are low (<12.1 nmol/l), it can lead to symptoms of hypogonadism such as decreased libido, decreased spontaneous erections, axillary and pubic hair loss, and impaired spermatogenesis with low or normal levels of inhibin B and concentrations of FSH and LH[13].

When a couple has regular sex intercourse for at least a year without taking contraception yet still is unable to conceive, this condition is considered a clinical limitation, known as infertility[14]. There are two types of infertility: primary and secondary infertility. Women classified as primary infertile are those who have never previously been clinically diagnosed as pregnant or as having the characteristics of infertility. On the other hand, women classified assecondary infertile are those who have been unable to experience clinical pregnancy but have previously been diagnosed with clinical pregnancy[15]. This also applies to men regarding their participation in the role of initiating pregnancy. In Indonesia, the prevalence of infertile couples was 15–25% in 2013. However, there was no data regarding the prevalence of infertility in men[16,17]. Due to the fact that male infertility is not a commonly reported disease, data on its prevalence is difficult to obtain. In addition, the costs of male infertility interventions are usually covered privately, hence not recorded in health insurance statistics[18]. Furthermore, some lifestyle-related determinants of infertility include frequency of sexual activity, dietary restriction and excessive exercise, stress, obesity, smoking, marijuana consumption, and alcohol consumption[14].

Infertility is an essential biomarker of overall health since it is useful as a marker of increased risk of comorbidities and mortality[19,20]. Furthermore, success in conceiving depends on the involvement of both spouses, including men, despite the common belief that infertile women are the cause of infertility. According to previous data, it was estimated that 35% of infertility cases were attributed to only women, 20% to both women and men, 30% to only men, and another 15% had unknown reasons[21]. This is also in line with previous data showing that 25–30% of total infertility cases are due to male infertilityof[12]. On a global scale, more than 40% of infertility cases are due to male infertility[22]. In addition, based on previous study, obese men had a higher prevalence of azoospermia and oligospermia (12.7% and 31.7%, respectively) compared to normal-weight men (9.8% and 24.5%)[23].

The authors conducted a literature review in light of the high prevalence, impact, or disadvantages of infertility, as well as the limited research on male infertility. This study further discussed and summarized several studies related to obesity and its association with male infertility, systematically based on existing rules. Therefore, it was expected that the results of this study would be used as a reference for intervention efforts or further research related to the issues discussed, which are obesity and male infertility, in an effort to minimize the losses that occur, both in terms of health, social, and economic.

METHODS

This study used a literature review method in its writing, drawing on the results of previous studies on the same topic as well as its data and/or findings. In order to generate an article that is pertinent to a certain topic or issue, a literature review is not the only source of main research; instead, it was also collected through surveys and literature research sourced from books, journals, and other publications related to the research topic[24]. The first stage of writing a literature review is selecting a review topic. The second stage is searching for and selecting relevant articles. The final stage is analyzing and synthesizing the literature. Moreover, the research data used was taken from the results of previous studies carried out between 2018 and 2023, or the last 5 years. The research reference used is original research or direct observational research (cross-sectional, case control, or cohort). Additionally, journal databases including Science Direct, Scopus, and PubMed served as the primary data sources. The reference search included the keywords "obesity," "infertile men," "infertility," "semen parameters," "obesity and semen quality," and "obesity and male infertility," in addition to specific names of markers of obesity and male infertility such as "leptin and infertility in men." The determination of keywords was based on the research objectives, which were to determine the association between male infertility and obesity, in which each keyword has a concept or meaning that is approximately similar and relevant. Furthermore, the inclusion criteria in this literature study are: literature that has undergone peer review and has proven that it is credible both nationally and internationally; original research with observational research designs (cross-sectional, case control, and cohort); and research topics related to obesity and infertility in men. Meanwhile, the exclusion criteria in the reference search included research results that are only available in abstract form and cannot be accessed in full text, as well as research on experimental animals. After an independent screening process and selection by one of the authors based on inclusion and exclusion criteria, 21 references were obtained, of which 8 were selected for review and adjusted to the topic discussed. The selection of eight articles was based on the systematic literature review method and adjusted to the predetermined inclusion criteria. The selection of articles was also carried out using the synthesis matrix technique based on the topic.

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Figure 1 shows the flow diagram of the literature search strategy used in this study.

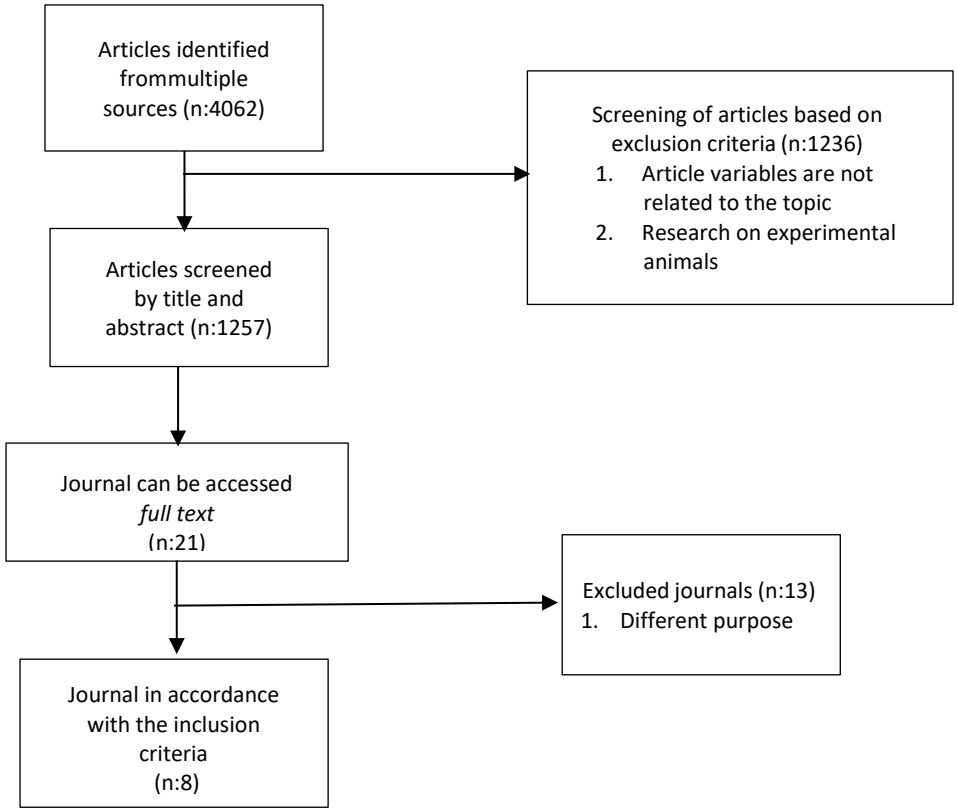

Image 1. Flow *diagram of literature search strategy*

DISCUSSION

Table 1 shows the results of previous studies on the association between obesity and infertility in productive-aged men. The results of the literature search found eight relevant articles. Five articles demonstrated that there was a relationship between male obesity based on measurements and sperm quality, quantity, and motility. Meanwhile, three articles discovered that there was no relationship between male obesity based on body mass index (BMI) measurements and sperm quality, quantity, and motility. This literature study has a limitation, which is in obtaining reference articles with respondents of a specific age, allowing variations in the research results in each article. Therefore, further research is required to include other factors that directly affect male infertility in light of increasing obesity rates and their effect on male infertility.

Association between Obesity and Male Infertility

In this literature study, the sperm parameters measured were limited to quantitative parameters (sperm volume, concentration, and sperm count) and qualitative parameters (sperm motility, morphology, and deoxyribonucleic acid (DNA)). There was a significant association found in five previous studies between obesity and infertility parameters in men. According to Zhang et al., increased BMI was associated with lower semen volume and sperm motility[25]. They explained that there are several mechanisms by which obesity affects sperm parameters. The excessive conversion of androgens to estrogens caused by obesity can lead to an increase in aromatase activity and subsequent reproduction; this imbalance ultimately results in lower-quality semen. In addition, there is an association between obesity and chronic inflammation and oxidative stress in the male reproductive tract, which can directly damage testicular tissue and sperm quality[26,27]. Furthermore, obesity increases scrotal temperature, and heat exposure can damage sperm[28]. According to research by Maghsoumi-Norouzabad et al., there was an association between men who are overweight and obese and a decrease in sperm count due to altered hormonal profiles[29]. This also aligns with three previous studies: the first by Ma et al. showing a significant association between obesity and sperm quality and quantity; the second by Oliveira et al. demonstrating an association between increasing BMI and sperm quality and quantity through mitochondrial damage and sperm concentration; and the third by Le, M.T., et al. showing an association between increasing BMI and sperm quality[30,31,32]. In contrast, three previous studies that investigated the relationship between obesity and infertility—specifically, a decrease in sperm parameters—did not provide any significant results. Nevertheless, the two previous studies discovered that there was no association between obesity and a quantitative decrease in sperm but identified specific associations in qualitative parameters such as motility, morphology, and sperm DNA. As in research conducted by Zhu et al., increasing BMI was associated with

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increased sperm apoptosis and sperm DNA damage[33]. According to research conducted by Bansal et al., an increase in BMI was associated with a decrease in sperm quality in the form of motility[34]. In addition, another study—that is, conducted by Alahmar et al.—did not find a significant association between obesity (BMI) and changes in sperm parameters, both qualitative and quantitative[35].

Two studies using cross-sectional designs and one study using a cohort design both did not demonstrate any significant results. There is still a need for studies regarding hormonal evaluation and DNA fragmentation tests to support the research process since inconsistent data collection in terms of age, time, and hormonal conditions that affect sperm changes might lead to insignificant research results. Therefore, based on the observational research literature studies that have been identified, it can be concluded that there was an increased risk of decreased sperm parameters, which suggests that men who have an increase in BMI or high BMI *(*obesity) are more likely to experience an increase in the degree of infertility.

Obesity and Changes in Sperm Quantity and Quality Parameters

Obesity can have a direct or indirect effect on male fertility through several mechanisms, including altered hormonal profiles. BMI increases in humans cause a reduction in plasma sex hormone-binding globulin (SHBG), which in turn leads to levels of testosterone decreasing and estrogen increasing[36]. Furthermore, due to the larger white adipose tissue, the obese state maintains high estrogen levels[29]. The enzyme cytochrome P450 aromatase is highly expressed in white adipose tissue and is responsible for a key step in estrogen biosynthesis. Due to the high availability of the aromatase enzyme, there is an increased conversion of androgens to estrogen. Moreover, high estrogen levels have a negative effect that can disrupt the process of spermatogenesis by controlling testosterone levels through negative feedback on the hypothalamus[29]. In addition, due to increased scrotal adiposity, obesity has also been reported to increase scrotal temperature. This can interfere with the spermatogenesis process and impair semen parameters, including decreased sperm count, concentration, and motility, as well as an increased DNA fragmentation index.

A decrease in excess inhibin B compared to a decrease in FSH suggests that obesity can also directly alter spermatogenesis and Sertoli cell function[29]. Moreover, Leydig cells are stimulated to synthesize testosterone by inhibin B[10]. Leydig cells, which are associated with testosterone in the formation of secondary genitalia such as Adam's apple, mustache, pubic hair, etc., and also support ABP in the process of spermatogenesis, are associated with a decrease in LH levels[10]. Furthermore, obesity has been reported to directly stimulate semen abnormalities through increasing production of ROS, inflammatory mediators that cause tissue damage[37,38], and inflammatory mediators that damage testicular and epididymal tissue. In addition, semen quality may be affected by increased levels of inflammatory mediators, including TNF-α and IL-6, and decreased levels of vascular endothelial growth factor (VEGF) in the semen plasma of obese men[39].

Several recent studies suggested that increased adiposity—which is related to changes in BMI and reproduction—may be the cause of epigenetic changes, such as sperm DNA methylation and non-coding ribonucleic acid (RNA) modifications[40]. Additionally, high plasma leptin levels are a direct result of obesity. Therefore, leptin synthesis, a key regulator of adipokines, generally occurs in white adipose tissue, and the serum of obese men typically contains high levels of this hormone[41]. Moreover, collective observations from human and animal studies suggest that leptin may have a role in the association between infertility and obesity. The statement is supported by the findings showing decreased sperm count, increased sperm abnormalities, oxidative stress, and elevated leptin levels in obese men[42,43]. Furthermore, leptin may act through receptors on KISS1 neurons that stimulate the release of GnRH from the hypothalamus. In this case, KISS1 neurons project to GnRH neurons and *neuropeptide Y* (NPY) neurons. Therefore, leptin can prevent the inhibition of GnRH by NPY neurons through KISS1. This ultimately affects gonadotropin release from the pituitary, reducing steroidogenesis and resulting in hypogonadotropic hypogonadism[36]. This adverse effect has been linked to increased leptin-induced oxidative stress and uncontrolled production of ROS, despite the fact that the main pathway causing this disorder remains unidentified[44]. At the physiological level, ROS are crucial in sperm maturation, capacitation, and the acrosome reaction. In addition, at the pathological level, ROS impairs testicular germ cell proliferation, which negatively affects sperm plasma membrane fluidity, impairs sperm motility, and increases sperm DNA damage[43].

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Table 1. Summary of literature selected

No.	Researcher	Title	Research Location	Methods	Findings
1.	(Alahmar et al., 2018)[35]	The impact of obesity on seminal fluid in men with infertility	Iraq	The method used in this research was cross-sectional, with a total of 74 respondents at the age not mentioned in the research.	• There were a total of 74 respondents, of which 30 had a normal weight (40.54%), 30 were overweight (40.54%), and 14 were obese (18.91%). • Obese men were shown to have lower sperm concentration; however, the difference was not significant when compared to normal weight and overweight infertile men. Furthermore, there was no significant difference observed in sperm progressive motility, total motility, or normal morphology among the three groups. • Obesity did not affect sperm concentration, motility, or normal morphology in infertile men since there was no significant association between obesity based on BMI (body mass index) and changes in sperm parameters, both quality and quantity.
2.	(Oliveira et al., 2018)[30]	Association between body mass index and sperm quality and sperm DNA integrity. A large population study	Finlandia	The method used in this research was cross-sectional, with a total of 1824 respondents at an undisclosed age.	• There were a total of 1824 respondents, of which 370 (20.3%) were underweight, 856 (46.9%) were normal weight, and 598 (32.8%) were obese. • High body mass index (BMI) had a negative effect on sperm concentration, vitality, motility, and morphology (p 0.05). In addition, increased body mass index (BMI) was associated with increased mitochondrial damage in spermatozoa (p < .05). • Increased body mass index (BMI) was associated with sperm quality (sperm concentration) and increased mitochondrial damage.
3.	(Ma et al., 2019)[32]	Association between BMI and semen quality: an observational study of 3966 sperm donors	China	The method used in this research was cross-sectional, with a total of 3966 respondents aged 22–46 years.	• There were a total of 3966 respondents, of which 222 were underweight (5.59%), 3046 were normal weight (76%), 660 were overweight (16.64%), and 38 were obese (0.95%). • Overweight was significantly associated with a 4.2% (1.6%, 6.8%), 3.9% (0.9%, 6.9%), and 3.6% (0.2%, 6.9%) decrease in semen volume, total sperm count, and total motile sperm count, respectively. • Overweight was significantly associated with lower semen volume, total sperm count, and total motile sperm count.
4.	(Zhang et al., 2019)[25]	The Negative Impact of Higher Body Mass Index on Sperm Quality and Erectile Function: A Cross-Sectional Study	China	The method used in this research was cross-sectional, with a total of 3174 respondents aged >18 years.	• There were a total of 3174 respondents, of which 5.4% were obese, 36.6% were overweight, 56.8% were of normal weight, and 1.2% were underweight.

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No.	Researcher	Title	Research Location	Methods	Findings
		Among Chinese Males of Infertile Couples			• Obesity was associated with lower semen volume, lower sperm motility, and erectile dysfunction in Chinese men from infertile couples.
5.	(Le, M.T., et al., 2020)[31]	Impact of body mass index and metabolic syndrome on sperm DNA fragmentation in males from infertile couples: A cross-sectional study from Vietnam	Vietnam	The method used in this research was cross-sectional, with a total of 290 respondents aged 30–40 years.	• There was a significant positive association between DNA fragmentation index (DFI) and body mass index (BMI). In the group of men classified as having a normal weight (defined as a BMI <23), the incidence of men with DFI <30 was 81.34%, whereas in the overweight group (defined as a BMI >23), it was only 69.87%. Among males who were overweight, 30.13% had a DFI >30, while the percentage of normal-weight men who had this condition was only 18.66%. • The research did not find any significant differences in semen parameters related to BMI due to the younger mean age and lower BMI in this research. • Overweight respondents showed a significant difference in their worse sperm DNA fragmentation results. This demonstrates the effect of BMI on sperm quality.
6.	(Maghsoumi-Norouzabad et al., 2020) [29]	The Impact of Obesity on Various Semen Parameters and Sex Hormones in Iranian Men with Infertility: A Cross-Sectional Study	Iran	The method used in this research was cross-sectional, with a total of 119 respondents at the age not mentioned in the research.	• There were a total of 119 respondents, of which 30 had normal nutritional status (25.21%), 56 were overweight (47%), and 33 were obese (27.7%). • The research found that overweight and obese infertile men had significantly lower sperm count, total motility, and progressive sperm based on body mass index (BMI) and waist circumference (WC) compared to normal-weight infertile men based on their waist circumference (WC). • In comparison to normal-weight men, being overweight or obese in men might exacerbate infertility.
7.	(Zhu et al., 2021)[33]	Association Between Body Mass Index and Male Sperm Apoptosis and Apoptosis-Related Factors	China	The method used in this research was cross-sectional, with 54 respondents aged 22–40 years.	• There were a total of 54 respondents, of which 16 (29.6%) had a normal body mass index (BMI), 17 (71.48%) were overweight, and 21 (38.8%) were obese. • Body mass index (BMI) was not significantly associated with age, duration of infertility, duration of sexual abstinence, semen volume, sperm concentration, or level of normal sperm morphology ($p > 0.05$). However, progressive sperm motility was significantly reduced, and the levels of DNA fragmentation index (DFI) and sperm apoptosis were significantly increased in overweight and obese men compared to men with a normal body mass index (BMI).

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No.	Researcher	Title	Research Location	Methods	Findings
8.	(Bansal et al., 2023)[34]	The effect of body mass index on semen quality	India	The method used in this research was a cohort, with a total of 221 respondents aged 30–40years.	• There were a total of 221 respondents, of which 5 (2.3%) had a BMI underweight, 49 (22.2%) were in the normal range, 49 (22.2%) were overweight, 85 (38.5%) were obese 1, and 33 people (14.9%) were obese 2. • The statistical results ($p<0.05$) indicated that obesity had a negative effect on volume, progressive motility, and total sperm motility. • Despite the fact that there was no statistically significant difference, overweight and obese men had decreased sperm concentrations compared to men with a normal body mass index (BMI). As BMI increased, there was a significant reduction in total motility. • Obesity causes a marked decrease in semen volume and motility. People with a BMI lower than normal are more likely to experience oligospermia.

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CONCLUSIONS

Based on the eight articles obtained, five articles showed a significant association between obesity and both quantitative and qualitative parameters in male infertility, while three articles did not show a specific association between increased BMI or obesity and changes in sperm parameters, which is quantity. Moreover, men with a high BMI or obesity are more likely to have decreased sperm parameters, which indicate a higher level of infertility. Obese men may be more susceptible to changes in sperm parameters, both quantitatively (volume, number, and concentration) and qualitatively (motility, morphology, and sperm DNA). Furthermore, direct observational studies can be conducted in Indonesia due to the increasing population with obesity and increasing infertility in men. Due to the fact that the prevalence of obesity is continuously increasing, there is a need for greater awareness of its effect on fertility and a deeper comprehension of the underlying mechanisms. This will allow for the implementation of appropriate nutritional interventions and management. In addition, the comprehension of male infertility due to obesity may potentially address the increased risk of comorbidities and mortality.

ACKNOWLEDGEMENTS

The author would like to thank Dr. Siti Rahayu Nadhiroh, S.KM., M.Kes as the supervisor of this writing for her advice and input so that the writing of this *literature review* can be completed properly.

Conflict of Interest and Funding Disclosure

All authors have no conflicts of interest in this research. This research was funded by private funds.

Author Contributions

ANPAP: conceptualization, investigation, methodology, writing–review and editing, writing–original draft; SRN: supervision, writing–review and editing.

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