The impact of obesity and metabolic health on male fertility: a systematic review

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The impact of paternal obesity and metabolic disease on semen quality and fertility outcomes is not fully appreciated. With increasing obesity rates, researchers have studied the intricate relationship between paternal body mass index, metabolic health, and male fertility. This systematic review identified 112 articles in the MEDLINE database between 2013 and 2023 that investigated the effects of body mass index, diabetes, metabolic syndrome, exercise, weight loss medication, or bariatric surgery on semen parameters, sperm quality, or fertility outcomes. This review suggests that obesity, diabetes, and metabolic syndrome have a negative impact on various parameters of male fertility, from semen quality to sperm deoxyribonucleic acid integrity. There is also mounting evidence that male obesity is correlated negatively with live births via both natural conception and assisted reproductive technologies. Lifestyle interventions, such as physical exercise, generally appear to improve male fertility markers; however, the type and intensity of exercise may play a crucial role. Pharmacologic treatments for weight loss, such as metformin and glucagon-like peptide 1 agonists, present a more complex picture, with studies suggesting both beneficial and detrimental effects on male reproductive health. Similarly, surgical interventions, such as gastric bypass surgery, show promise in improving hormonal imbalances but have mixed effects on semen parameters. Future research is needed to clarify these associations and inform clinical guidelines. In the interim, health practitioners should incorporate these insights into clinical practices, encouraging proactive lifestyle changes and providing targeted treatments to improve male reproductive health. (Fertil Steril® 2023;120:1098–111. ©2023 by American Society for Reproductive Medicine.)

Key Words: Obesity, body mass index, metabolic syndrome, male fertility, semen parameters

Male factor infertility is a contributing factor in approximately 30%–40% of couples with infertility and is the primary factor in 20% of cases (1, 2). Semen quality is linked to paternal health through genetic, environmental, and lifestyle factors (3, 4). Over the last several years, there has been growing interest in identifying modifiable risk factors for poor semen quality. Mainstream media has reported that male sperm counts have been declining over the past 50 years, highlighting a public health concern (5, 6). Although there is still active debate over the validity and significance of these claims, the center of this concern is the growing consensus that environmental factors play a critical role in male fecundity. Poor semen quality has been reported from environmental factors such as air pollution, pesticides, industrial chemicals, and exposure to excessive heat (7). There is also mounting evidence that other intrinsic markers of health, such as obesity, metabolic disease, and sedentary lifestyle, are also implicated in male factor infertility. This is a timely topic because the male obesity rates are increasing in the Western society, with 40% of men in reproductive ages being considered obese on the basis of body mass index (BMI) (8). In this article, we review existing data on the impact of obesity and metabolic health on male semen parameters and fertility outcomes.

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MATERIALS AND METHODS

A systematic review was conducted as guided by the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (9). A search of the current literature was performed on the MEDLINE database to identify human trials related to male physical and metabolic health with relation to fertility. Keywords included "obesity," "body mass index," "metabolic syndrome," "diabetes," "insulin resistance," "exercise," "weight loss," "bariatric surgery," and "male fertility" or "semen parameters." The search was conducted in June 2023 and included studies from the last 10 years (2013–2023). We chose to focus our review on articles published after 2013 to capture the most recent advancements and findings in the field, ensuring that our analysis reflects the current understanding and state-of-the-art knowledge on the impact of obesity on male fertility. A total of 1,629 relevant abstracts were screened

for inclusion. The inclusion criteria were retrospective and prospective human studies that reported clinical semen parameters or fertility outcomes. The exclusion criteria were nonhuman or in vitro studies. A total of 1,517 articles were excluded. The remaining 112 articles were included for thorough examination and review (Fig. 1).

Semen Parameters as a Surrogate of Male Reproductive Potential

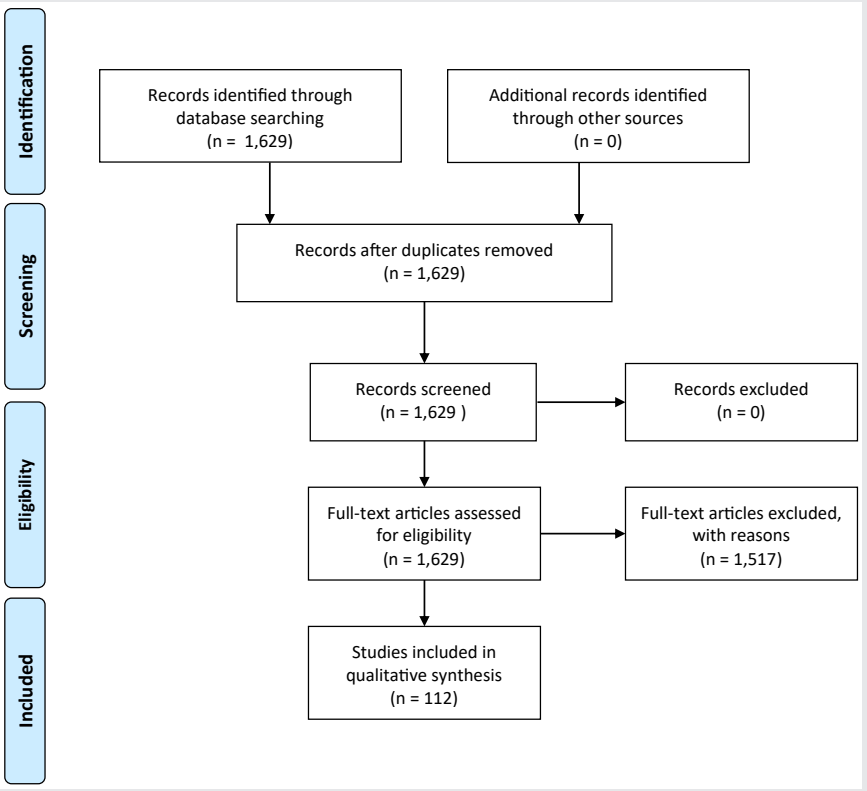
Semen analyses have been the cornerstone of the male factor fertility evaluation for over a century. Since the discovery of sperm in 1677 by Antonie van Leeuwenhoek, our understanding of sperm physiology and semen parameters has expanded considerably (10). The modern semen analysis took form with work from William Cary in 1916. The first reference values for sperm concentration were later published in a study of 300 men by Macomber and Sander in 1929 (10). Over the last century, there has been considerable effort to harmonize techniques and reporting across andrology laboratories (11).

Normal semen parameters have been established by the World Health Organization via large, multinational studies that analyzed 3,589 semen samples from fertile men (11). Study participants were deemed fertile on the basis of a documented pregnancy with their partner in less than 12 months of trying to conceive. The reported value for normal sperm concentration is >15 million/mL of ejaculate. Given normal semen parameters, approximately 75% of couples will achieve pregnancy in 6 months, and 85% will conceive within the first year (1, 12). Other markers of sperm quality, such as sperm motility, strict morphology, teratozoospermia index, acrosome index, deoxyribonucleic acid (DNA) fragmentation, oxidative stress, and epigenetic changes, have also been differentiated between fertile and subfertile couples (13). Despite a robust understanding of sperm parameters and semen quality, these qualitative and quantitative measures are still not perfect surrogates for male fertility potential. As such, we not only focus our review on the impact of semen quality but also summarize the impact of obesity and metabolic syndrome on other markers of sperm quality.

IMPACT OF OBESITY AND METABOLIC SYNDROME ON MALE FERTILITY

Obesity is thought to impair male fertility through multiple mechanisms. There is a direct impact on the hypothalamic-pituitary-gonadal axis by peripheral aromatization leading to hypogonadotropic hyperestrogenic hypogonadism (14). Obesity may also negatively impact spermatogenesis through endocrine disruptors such as insulin, leptin, cortisol,

FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram of systematic literature search.

Service. Impact of obesity on male fertility. Fertil Steril 2023.

cytokines, adipokines, and other chronic inflammatory states (15). Another mechanism is gonadal temperature dysregulation due to increased hip, abdominal, and scrotal fat tissues. There are also indirect complications of obesity brought about by comorbid conditions such as cardiovascular disease, type 2 diabetes mellitus (DM), and erectile dysfunction. These mechanisms are summarized in Figure 2.

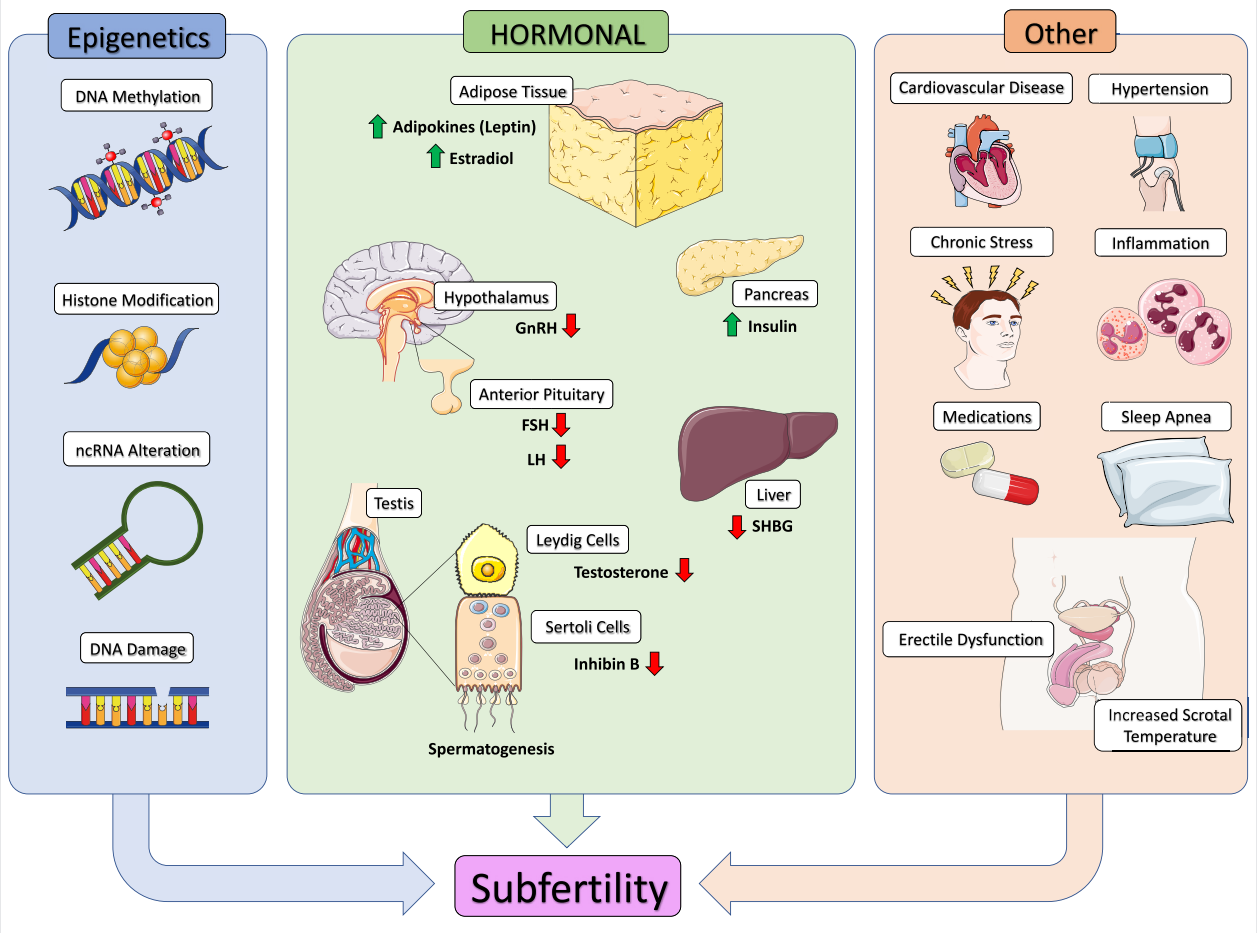
Association Between Obesity and Male Fertility

Prior systematic reviews have indicated that there is an association between obesity and male factor infertility (16, 17). Campbell et al. (16), in a robust systematic review and meta-analysis of 30 studies and 115,158 participants, concluded that obese males were more likely to experience infertility than their nonobese counterparts (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.53–1.79). Santi et al. (17), in their recent systematic review and meta-analysis of 28 studies, also concluded that obese men had lower sperm concentration, total sperm number, progressive motility, and normal morphology than their normal-weight counterparts. The following subsections will examine the impact of obesity on semen parameters, sperm DNA integrity, epigenetic modifications, and conception rates in natural and assisted reproductive technology (ART) outcomes.

Obesity and semen parameters. The impact of obesity on semen parameters has been well studied. Thirty studies were identified that analyzed surrogates of obesity (BMI, weight, waist circumference, and bioelectric impedance analysis) and semen parameters. Of the 30 studies, 25 showed a correlation between increasing BMI and worsening semen parameters (sperm concentration, volume, total motile sperm, and morphology).

One of the largest series was an observational study with 29,949 semen samples collected over a 5-year period conducted by Ma et al. (18). They categorized BMI into four

FIGURE 2



Proposed mechanisms of obesity and metabolic syndrome related male factor infertility. DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; LH = luteinizing hormone; ncRNA = noncoding ribonucleic acid; SHBG = sex hormone-binding globulin. (Figure modified with text, markings, and annotation after adaptation from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.)

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groups (underweight, <18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; and obese, ≥ 30 kg/m^2). They found that both underweight and overweight individuals showed significant decreases in sperm parameters. Namely, underweight individuals had reductions in sperm concentration (3.0% reduction; 95% CI, 0.1%–5.8%), total sperm number (6.7% reduction; 95% CI, 1.9%–11.3%), and total motile sperm count (7.4% reduction; 95% CI, 2.2%–12.4%). Overweight individuals had reductions in semen volume (4.2% reduction; 95% CI, 1.6%–6.8%), total sperm number (3.9% reduction; 95% CI, 0.9%–6.9%), and total motile sperm count (3.6% reduction; 95% CI, 0.2%–6.9%). This suggests that the fertility of both underweight and overweight individuals is impacted negatively by their weight.

Eisenberg et al. (19) conducted a prospective cohort study of 501 couples with infertility and found that overweight and obese individuals (BMI, 25.0–29.9, overweight, and >30.0, obese) were associated with a higher prevalence of low ejaculate volume, sperm concentration, and total sperm count. Belan et al. (20), in a cross-sectional study of 97 couples with infertility, reported that BMI ($P=.026$) and waist circumference ($P=.049$) were associated negatively with the percentage of progressive motile sperm.

Several studies have failed to demonstrate a significant relationship between BMI and semen parameters, resulting in many systematic reviews not observing any differences. Our current review identified five negative studies. For example, MacDonald et al. (21) performed a cross-sectional study of 511 men presenting to New Zealand fertility clinics. They found that overweight and obese BMIs showed no associated increased relative risk of abnormal semen analysis; however, multiple limitations include 15% of BMIs being self-reported, not controlling for time of abstinence, a median age of 36.8 years, 72.8% of individuals being overweight or obese, and uncontrolled reasons for the individual fertility evaluation. Despite a handful of negative studies, the abundance of evidence suggests a link between obesity and poor semen parameters.

Obesity and sperm DNA integrity. Mounting evidence suggests a relationship between male obesity and increased sperm DNA fragmentation (SDF); however, the data are still inconclusive. We reviewed a total of 13 studies. There were eight articles suggestive of a correlation and five articles without a correlation. Sepidarkish et al. (22) conducted a meta-analysis in 2020 comparing BMI and SDF in 14 studies totaling 8,255 men. Three of the studies reported higher SDF levels in obese men than in normal weight individuals (standardized mean difference, 0.23; 95% CI, 0.01–0.46; $P=.05$; $I^2 = 0$); however, they concluded that there were insufficient data to support a strong association between BMI and SDF.

Dupont et al. (23) conducted a multicenter study of 330 men in subfertile couples and compared DNA fragmentation and sperm morphology across different cohorts on the basis of BMI. The DNA fragmentation rates were significantly higher in the obese group (mean difference, 3.9; 95% CI, 0.2–7.6) but not in the overweight group (mean difference, 1.1; 95% CI, −1.4 to 3.6).

Multiple studies have investigated other markers of sperm DNA compromise, such as seminal oxidative damage. Pearce et al. (24), in a small pilot study of 37 men, showed a positive correlation between BMI and sperm DNA oxidative damage using seminal 8-hydroxy-2′-deoxyguanosine. They also showed a positive correlation with BMI and SDF using the Halosperm test. Taha et al. (25) conducted a cross-sectional, case-control cohort study of 165 men who were deemed fertile on the basis of prior pregnancy in the last 12 months. These fertile men were divided into three cohorts on the basis of BMI. They then examined semen parameters, seminal reactive oxygen species (ROS) (chemiluminescent assay), sperm vitality (hypo-osmotic swelling test), and SDF. An increased BMI was correlated positively with the SDF percentage ($r = 0.799$, $P=.001$) and seminal ROS ($r = 0.673$, $P=.001$). Obesity was also correlated with lower sperm concentration ($r = -0.091$, $P=.014$), progressive sperm motility ($r = -0.697$, $P=.001$), normal sperm morphology ($r = -0.510$, $P=.001$), and sperm vitality ($r = -0.586$, $P=.001$).

There were five articles that did not show a positive correlation with BMI and SDF. Eisenberg et al. (19), in their prospective cohort study of 501 couples with infertility, did not find a relationship between BMI or waist circumference and DNA fragmentation. Oliveira et al. (26) collected semen samples from 1,824 men who underwent infertility workup and examined the impact of BMI on semen parameters, sperm morphology, SDF, chromatin packaging/underprotamination, mitochondrial damage, and apoptosis. They found that BMI affected negatively sperm concentration, vitality, motility, and morphology ($P<.05$). There was also increased mitochondrial damage in the obese patients; however, they did not find a significant impact of BMI on SDF, sperm protamination, or sperm apoptosis ($P>.05$).

Obesity and epigenetic modifications. In addition to the direct adverse effects of obesity on male fertility, there is mounting evidence that adverse effects may be transmitted to male offspring via genetic and epigenetic alterations to germ cell DNA. We reviewed 4 articles that examined the effects of obesity on sperm epigenetics.

Two studies investigated sperm DNA methylation compared with BMI (27, 28). Soubry et al. (27) investigated sperm DNA methylation in 69 men and identified differentially methylated regions (DMRs) in normal weight vs. overweight and obese participants (specifically MEG3-IG DMR and H19 DMR). Keyhan et al. (28) included 67 men in their recent investigation on sperm DNA methylation and found that overweight and obese individuals had differences in mature spermatozoa DNA methylation profiles relative to controls with normal BMI. They identified 3,264 CpG sites in human sperm that are associated significantly with BMI.

Pini et al. (29) studied the sperm proteome for five normal weight individuals and five obese individuals. They identified 2,034 proteins and found significantly altered abundance in 27 of those proteins. The altered proteins were involved in a variety of biologic processes, including oxidative stress (GSS, NDUFS2, JAGN1, USP14, and ADH5), inflammation (SUGT1 and LTA4H), translation (EIF3F, EIF4A2, and

CSNK1G1), DNA damage repair (UBEA4), and sperm function (NAPA, RNPEP, and BANF2).

Raee et al. (30), in their recent cohort study of 64 healthy men, examined sperm telomere length, autophagy-related messenger ribonucleic acid levels (Beclin1, AMPKa1, ULK1, BAX, and BCL2), SDF index, sperm chromatin maturation assay, intracellular ROS levels, and sperm viability/apoptotic changes in men with either normal (18.5–25 kg/m^2) or obese ($\geq$30 kg/m^2) BMI. Obesity was related to a marked reduction in the relative sperm telomere length. There was considerable up-regulation of Beclin1, ULK1, and BCL2 in the obese group. Obesity was also associated with decreases in the semen volume, total sperm count, progressive motility, and viability; higher percentages of DFI, sperm with immature chromatin, and late-stage apoptosis; and elevated ROS levels.

Obesity and natural conception: ART outcomes. The impact of obesity on conception and live birth rates was explored for both natural conception and ART. We identified 16 articles that evaluated male BMI and fertility outcomes. Campbell et al. (16) determined that an obese male partner was associated with a 10% absolute risk of having a nonviable pregnancy. They also determined that obese men were less likely to have successful live birth with ART while controlling for female BMI, with a reported reduction in live birth per cycle with an OR of 0.65 (95% CI, 0.44–0.97).

Multiple articles showed a correlation between increased BMI and worse ART outcomes. Petersen et al. (31) conducted one of the largest series in their 2013 population-based cohort using the Danish national registry with 12,566 couples with infertility who underwent 25,191 cycles of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). They found that a higher male BMI negatively impacted the live birth rates after IVF treatments (OR, 0.73; 95% CI, 0.48–1.11); however, with ICSI, the correlation was less clear. Umul et al. (32) conducted a prospective cohort study with 155 couples with infertility who underwent ICSI. They found that paternal obesity had a significant negative impact on the clinical pregnancy rate (P=.04) and live birth rate (P=.03). For context, the US fetal mortality rate stands at 5.74, providing a comparative baseline against which the nonviable pregnancy rates for nonobese men can be evaluated (33). This study supports the idea that an increasing paternal BMI has a negative influence on the clinical pregnancy and live birth rates for ICSI patients. Liu et al. (34) examined 11,191 couples with infertility who underwent ART (6,569 first cycles) and investigated the relationship between paternal BMI and live birth, clinical pregnancy, pregnancy loss, available embryos, high-quality embryos, and fertilization rates. They found that overweight and obese couples had lower numbers of available embryos, fewer high-quality embryos, and lower fertilization rates; however, neither male or female BMI affected the clinical pregnancy, live birth, or pregnancy loss rate. Notably, this was a Chinese cohort with adjusted BMI standards according to the Chinese Obesity Working Group (normal, 18.5–23.9 kg/m^2; overweight, 24–27.9 kg/m^2; and obesity, $\geq$28 kg/m^2).

Alternatively, six articles showed no correlation between obesity and fertility outcomes. For example, Arabipoor et al. (35) did a retrospective cohort study of 990 couples with infertility who underwent ART and found that an increased male BMI had no impact on live births with ICSI. Schliep et al. (36) conducted a cross-sectional study of 721 couples with infertility who underwent ART. They found that the live birth, clinical pregnancy, spontaneous abortion, and therapeutic abortion rates were not associated with male or female BMI.

Some of the studies had mixed findings. Hoek et al. (37) found an inverse association between the paternal BMI and fertilization rate but not the live birth rate. Merhi et al. (38) investigated 344 couples with infertility who used ART and found that male obesity was associated with a lower chance for clinical pregnancy after IVF (OR, 0.17; 95% CI, 0.04–0.65; P=.01) but not after ICSI cycles (OR, 0.88; 95% CI, 0.41–1.88; P=.75) (Table 1).

Association Between Metabolic Health and Male Fertility

The impact of male physical health on fertility has been explored through two indicators of poor metabolic health, namely, type 2 DM and a diagnosis of metabolic syndrome. Diabetes and metabolic syndrome portend a poor prognosis with respect to male fertility. We identified 32 articles that investigate the correlation between poor metabolic health and poor male fertility.

Diabetes and male fertility. The impact of diabetes on fertility remains to be determined. Twelve articles suggested a correlation between DM and poor semen parameters or reproductive hormones. AbbasiHormozi et al. (39) evaluated 40 healthy controls and 40 obese, 35 lean-DM, and 35 obese-DM individuals in a prospective study in 2023. Sperm motility, progressive motility, sperm count, and sperm morphology were found to be lower in the obese-DM (P =.001), lean-DM (P =.01), and obese (P =.001) groups than in the control group. The obese-DM (P =.001) and obese (P =.011) groups had lower mean sex hormone-binding globulin levels than the control group.

There is also evidence that diabetes may impact SDF. Belladelli et al. (40) conducted a cross-sectional study in 2022 with 726 white European men with primary infertility. They measured serum hormones and SDF in every patient. A total of 339 men (46.6%) had a triglyceride/glucose index suggestive of insulin resistance (IR), and 154 (21.2%) had a homeostatic model assessment index of IR suggestive of IR. The homeostatic model assessment index is a method used to quantify IR and β-cell function. Men with a triglyceride/glucose index of >8.1 had a higher risk of SDF and nonobstructive azoospermia. Lu et al. (41) also found a positive correlation between inflammatory markers in semen (interleukin-17 and interleukin-18 levels) and SDF among individuals with DM. Thirty patients with DM and 30 healthy patients were evaluated. Semen parameters were analyzed for all patients. Males with DM had a lower percentage of sperm progressive motility, sperm vitality, sperm survival rate, the

TABLE 1

Studies on the association between obesity and male fertility.

Investigators	Study design	Participants	Findings
Semen parameters			
Ma et al. (18), 2019	Observational	3,966 sperm donors and 29,949 semen samples	Overweight was associated significantly with lower semen volume, total sperm count, and total motile sperm count. Underweight was associated significantly with lower sperm concentration, total sperm count, and total motile sperm count.
Belan et al. (20), 2019	Cross-sectional	97 men in couples with infertility	BMI and waist circumference were associated negatively with the percentage of progressively motile sperm. BMI, fruit and vegetable consumption, and hours of sleep were associated with increased total motile sperm count.
Eisenberg et al. (19), 2014	Prospective cohort	501 men in couples with infertility	Overweight and obesity were associated with a higher prevalence of low ejaculate volume, sperm concentration, and total sperm count.
MacDonald et al. (21), 2013	Cross-sectional	511 men in couples with infertility	Overweight and obesity showed no associated increased relative risk of abnormal semen parameters.
Sperm DNA integrity			
Dupont et al. (23), 2013	Prospective cohort	330 men in couples with infertility	The DNA fragmentation rate was significantly higher in obese men.
Pearce et al. (24), 2019	Pilot study	37 men with infertility	Positive correlation between BMI and sperm DNA oxidative damage (seminal 8-OHdG) and SDF (Halosperm).
Oliveira et al. (26), 2017	Cross-sectional	1,824 men presenting for infertility workup	BMI negatively affects sperm concentration, vitality, motility, and morphology. A high BMI is not associated with impaired sperm DNA integrity, DNA fragmentation, sperm protamination, or sperm apoptosis. A high BMI is associated with increased mitochondrial damage in sperm.
Taha et al. (25), 2016	Cross-sectional, case-control cohort	165 fertile men	Obese fertile men had significantly lower sperm concentration, progressive sperm motility, and sperm normal morphology, with significantly higher seminal ROS and SDF than fertile normal weight men and overweight men.
Eisenberg et al. (19), 2014	Prospective cohort	501 men in couples with infertility	Overweight and obesity were associated with a higher prevalence of low ejaculate volume, sperm concentration, and total sperm count. No relationship between BMI or waist circumference and DNA fragmentation.
Epigenetic modifications			
Raee et al. (30), 2023	Prospective cohort	64 healthy men	Obesity was related with a marked reduction in relative sperm telomere length. There was considerable up-regulation of Beclin1, ULK1, and BCL2 in the obese group. Obesity was also associated with a decrease in the semen volume, total sperm count, progressive motility, and viability; higher percentages of DFI, sperm with immature chromatin, and late-stage apoptosis; and increased ROS levels.

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TABLE 1

Continued.

Investigators	Study design	Participants	Findings
Pini et al. (29), 2020	Prospective cohort	10 semen samples	Significantly altered abundance in 27 proteins, involved in a variety of biologic processes, including oxidative stress (GSS, NDUFS2, JAGN1, USP14, and ADH5), inflammation (SUGT1 and LTA4H), translation (EIF3F, EIF4A2, and CSNK1G1), DNA damage repair (UBEA4), and sperm function (NAPA, RNPEP, and BANF2).
Keyhan et al. (28), 2021	Exploratory analysis	67 men	Overweight and obesity are associated with differences in mature spermatozoa DNA methylation profiles relative to controls with normal BMI. Identified 3,264 CpG sites in human sperm that are associated significantly with BMI.
Soubry et al. (27), 2016	Prospective cohort	69 men	Identified DMRs in normal weight vs. overweight and obese participants (MEG3-IG DMR and H19 DMR).
Natural conception and ART outcomes			
Petersen et al. (31), 2013	Population-based cohort	12,566 couples with infertility who underwent 25,191 IVF/ICSI cycles	An increased male BMI negatively influenced live birth after IVF treatments. With ICSI, the association with BMI was less clear.
Arabipoor et al. (35), 2019	Cross-sectional	990 couples with infertility who underwent ICSI	An increased male BMI had no impact on live births with ICSI.
Hoek at al. (37), 2022	Prospective cohort	211 couples with infertility who underwent ART	Inverse association between paternal BMI and fertilization rate but not with the live birth rate after adjusting for confounders. A higher paternal BMI was associated with faster development of the preimplantation embryo. Embryo quality was not altered.
Liu et al. (34), 2023	Retrospective cohort	11,191 couples with infertility who underwent ART	Overweight and obese couples had lower numbers of available embryos, fewer high-quality embryos, and lower fertilization rates; however, neither male or female BMI affected the clinical pregnancy, live birth, or abortion rate.
Umul et al. (32), 2015	Prospective cohort	155 couples with infertility who underwent ICSI	An increased BMI has a negative impact on ICSI success, including the live birth and clinical pregnancy rates. Paternal obesity was also a significant negative factor for sperm concentration and sperm motility.
Schliep et al. (36), 2015	Cross-sectional	721 couples with infertility who underwent ART	BMI is not associated with IVF success after accounting for male and female age, partner BMI, and parity.
Merhi et al. (38), 2013	Retrospective cohort	344 couples with infertility who underwent ART	Male obesity was associated with a decreased clinical pregnancy rate after IVF; however, embryo quality was not affected.

Note: BMI = body mass index; DMR = differentially methylated region; DMR = differentially methylated region, DNA = deoxyribonucleic acid; 8-OHdG = 8-hydroxy-2′-deoxyguanosine; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; ROS = reactive oxygen species; SDF = sperm deoxyribonucleic acid fragmentation.

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TABLE 2

Studies on the association between metabolic health and male fertility.

Investigators	Study design	Participants	Findings
Diabetes			
Belladelli et al. (40), 2022	Cross-sectional cohort	726 men with infertility	Approximately half of men with primary infertility had triglyceride/glucose indices suggestive of insulin resistance. Men with insulin resistance had worse hormonal and semen parameters.
Boeri et al. (42), 2018	Prospective cohort	744 men with infertility	Men with infertility with prediabetes had lower circulating testosterone and SHBG levels but higher FSH values and rates of impaired DFI than men with infertility without prediabetes.
La Vignera et al. (43), 2015	Prospective cohort	32 men with diabetes	Patients with DM1 had a lower percentage of spermatozoa with progressive motility, impaired mitochondrial function, and epididymal postejaculatory dysfunction.
AbbasiHormozi et al. (39), 2023	Prospective cohort	150 men	Metabolic changes, hormonal dysfunction, and inflammatory disturbance may be suspected mechanisms of subfertility in obese and subfertile men with diabetes.
Metabolic syndrome			
Leisegang et al. (45), 2014	Case-control pilot	54 men	Men with metabolic syndrome showed significant reductions in sperm concentration, total sperm count, total motility, sperm vitality, mitochondrial membrane potential, free testosterone, and free progesterone. The values for DNA fragmentation increased in the metabolic syndrome cohort.
Ventimiglia et al. (47), 2016	Cross-sectional	1,337 men with infertility	Patients with metabolic syndrome were older and had higher Charlson Comorbidity Index scores and lower levels of total testosterone, SHBG, inhibin B, and AMH. They were hypogonadal at a higher rate but did not differ significantly in semen parameters.
Chen et al. (46), 2019	Cross-sectional	8,395 men	Metabolic syndrome was associated with reduced normal morphology and sperm progressive motility.

Note: AMH = antimüllerian hormone; DM1 = type 1 diabetes mellitus; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; SHBG = sex hormone-binding globulin.

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TABLE 3

Studies on the impact of obesity management on male subfertility.

Investigators	Study Design	Participants	Findings
Exercise			
Mínguez-Alarcón et al. (52), 2014	Observational	215 men presenting to fertility clinic	No significant relationship was found between overall physical activity and semen quality. However, the study noted that men who engaged in outdoor activities had a higher percentage of normal sperm morphology.
Gaskins et al. (49), 2015	Observational	189 young men	Men in the highest quartile of moderate-to-vigorous activity had a 73% higher sperm concentration than those in the lowest quartile. Conversely, men who watched more than 20 h of TV per wk had a 44% lower sperm concentration than those who did not watch TV.
Hajizadeh Maleki et al. (50), 2017	Randomized controlled clinical trial	280 healthy men	Moderate-intensity continuous training significantly improved the markers of oxidative stress and inflammation in semen samples. However, high-intensity interval training and strength training modalities did not show similar improvements.
Maleki et al. (51), 2017	Randomized controlled clinical trial	433 men with infertility	The exercise group reported significantly attenuated inflammatory biomarkers, oxidative stress, and antioxidants. These changes coincided with favorable improvements in semen parameters, sperm DNA integrity, and pregnancy rate.
Lalinde-Acevedo et al. (48), 2017	Observational	32 healthy men	Semen volume, viability, progressive motility, total motility, normal morphology, and moribund cells were higher in the physically active group; however, sperm DNA damage, lipid peroxidation, and mitochondrial potential were not significantly different between the groups.
Weight loss medication			
Fontoura et al. (55), 2014	Case report	1 man	Case of a 35-y-old man on GLP-I RA liraglutide and experiencing primary and idiopathic infertility for 1 y.
Raghif et al. (53), 2016	Observational	18 obese men	Significant decrease in sperm count and sperm activity after 12 wk of treatment with metformin.
Zaidi et al. (54), 2017	Observational	100 men with diabetes	Sperm analysis revealed a notable increase in the total sperm count for insulin-dependent men with diabetes. However, their sperm motility was 10%–15% lower than metformin users, whereas 6% more metformin users showed improved sperm morphology compared with insulin-dependent men with diabetes.
Andersen et al. (56), 2022	Randomized controlled clinical trial	56 obese men	Men who participated in an 8-wk low-calorie diet saw improvements in sperm concentration and count. These enhancements persisted for 1 y in those who maintained their weight loss; however, other semen parameters, such as volume and motility, remained unchanged.
Surgery: gastric bypass			

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TABLE 3

Continued.

Investigators	Study Design	Participants	Findings
Legro et al. (57), 2015	Observational	6 obese men	After RYGB surgery, the testosterone levels significantly increased and remained elevated, and the serum SHBG levels also increased. Despite these hormonal changes and substantial weight loss, no significant alterations were observed in urinary estrogen metabolites, serum estradiol levels, semen parameters, or male sexual function.
Samavat et al. (60), 2018	Clinical trial	31 morbidly obese men	After BS, there was a significant improvement in sex hormones and certain semen parameters (semen volume and viability). After surgery, there was a reduction in the seminal interleukin-8 levels and SDF, whereas nonoperated individuals saw an increase in these parameters. The substantial weight loss from BS was correlated with improvements in several semen parameters.
Carette et al. (61), 2019	Randomized controlled clinical trial	46 obese men	Patients who underwent BS had a decrease in the total sperm count at 12 mo after surgery. However, this reduction was accompanied by a resolution of hypogonadism and decreased SDF in most patients over time. There was a decrease in the mean total sperm count after 1 y.
Wood et al. (58), 2020	Observational	74 men	In a subset of patients who underwent BS, researchers saw a more than twofold increase in the testosterone levels, an improvement in SDF, but a decrease in sperm concentration and total ejaculated sperm count. No changes were noted in patients who did not undergo surgery, concluding that although BS improves the reproductive hormone levels and SDF, it negatively affects sperm concentration.
Razzaq et al. (62), 2021	Case series	2 men after BS	A 30-y-old man with a BMI of 81.2 underwent BS and subsequently noticed changes in semen consistency and developed azoospermia, despite having a child previously. Similarly, a 48-y-old man with a BMI of 52, who already had three children, experienced azoospermia 1 y after the surgery.
Miñambres et al. (63), 2022	Case series	12 men who underwent BS	Obesity surgery led to significant weight loss and improved hormonal and erectile function in a study of 12 men; however, there was a notable decrease in the proportion of sperm cells with normal morphology 18 mo after surgery.

Note: BMI = body mass index; BS = bariatric surgery; DNA = deoxyribonucleic acid; GLP-I RA = glucagon-like peptide 1 receptor agonist; RYGB = Roux-en-Y; SDF = sperm deoxyribonucleic acid fragmentation; TV = television.

Service. Impact of obesity on male fertility. Fertil Steril 2023.

rate of normal sperm morphology, semen volume, and semen pH and density than the controls ($P<.05$).

Boeri et al. (42) analyzed 744 men with infertility in a prospective study in 2018. Semen analysis was completed, and serum hormones were measured for every man. In their population, 114 men (15.4%) had prediabetes. They found that older age, follicle-stimulating hormone, and idiopathic nonobstructive azoospermia (all $P\leq.04$) were all associated significantly with positive prediabetes status.

Interestingly, type 1 DM (DM1) also appears to be associated with poor semen parameters. A prospective study by La Vignera et al. (43) evaluated 32 patients with DM1 and 20 age-matched fertile men. Patients with DM1 had a lower percentage of progressive motility ($P<.01$) and higher percentage of spermatozoa with abnormal mitochondrial function than controls ($P<.01$). Didymo-epididymal ultrasound evaluation before and after ejaculation revealed that patients with DM1 also had greater signs of epididymal postejaculatory dysfunction than the controls.

Metabolic syndrome and male fertility. Metabolic syndrome is a group of interrelated conditions that places an individual at a heightened risk of adverse cardiovascular disease, stroke, and diabetes (44). Multiple definitions with different criteria have been proposed to diagnose metabolic syndrome; however, the most commonly used definitions encountered in our search were the National Cholesterol Education Program Adult Treatment Panel III criteria, International Diabetes Federation criteria, American Heart Association/National Heart, Lung, and Blood Institute criteria, and harmonized criteria of 2009. The criteria include IR, obesity, increased triglyceride level, low high-density lipoprotein level, and hypertension. We identified 20 articles that specifically evaluated the relationship between a diagnosis of metabolic syndrome and male factor infertility. The strength of association between metabolic syndrome and infertility was mixed. Fourteen articles showed a positive association, and six articles did not show a significant correlation between metabolic syndrome and infertility.

Leisegang et al. (45) conducted a case-control pilot study with 54 men that were divided into men with metabolic syndrome (n = 26) and healthy controls (n = 28). They then evaluated the semen parameters and reproductive hormone levels. The metabolic syndrome group had significantly lower sperm concentrations ($P=.0026$), total sperm counts ($P=.0034$), total motility ($P=.0291$), sperm vitality ($P=.002$), free testosterone levels ($P=.0093$), and free progesterone levels ($P=.0130$). This pilot study suggested a strong link between metabolic syndrome and fertility parameters.

Chen et al. (46) conducted a cross-sectional study of 8,395 Taiwanese men who underwent routine medical screening and determined the presence of metabolic syndrome using the National Cholesterol Education Program Adult Treatment Panel III criteria with the Asian cutoff for waist circumference. Semen parameters were evaluated for all men, and they found that metabolic syndrome was associated significantly with reduced normal morphology and sperm progressive motility.

Another large series was a cross-sectional study of 1,337 men evaluated for infertility by Ventimiglia et al. (47) in 2016. They compared semen parameters, scrotal ultrasound, and serum reproductive hormones for men with infertility with metabolic syndrome and men with infertility without metabolic syndrome. They concluded that 1 of 10 white European men presenting for infertility evaluation met the criteria for metabolic syndrome. Men with metabolic syndrome had lower levels of total testosterone ($P<.001$), sex hormone-binding globulin ($P=.004$), inhibin B ($P=.03$), and antimüllerian hormone ($P=.009$). Interestingly, they were hypogonadal at higher rates ($P<.001$) but did not differ significantly in semen parameters (Table 2).

IMPACT OF OBESITY MANAGEMENT ON MALE SUBFERTILITY

Mounting evidence suggests a relationship between male physical health and reproductive potential. There is also evidence suggesting that improving physical health through exercise, diet, medical management, and bariatric surgery may improve male fecundity. We reviewed 19 articles that examined this relationship.

Impact of Exercise on Semen Parameters

The interrelation between physical activity and male reproductive health, especially semen parameters, has been a focal point of numerous scientific investigations. We identified eight studies that explored this relationship. Seven of these studies suggest a correlation between exercise and male fertility. Several key themes and trends emerge from the given data.

A recurring theme in several studies is the comparison between physically active men and their sedentary counterparts. Lalinde-Acevedo et al. (48) performed an observational study of 32 men that demonstrated that physically active participants exhibited better semen parameters, such as volume, viability, progressive motility, and normal morphology, than the sedentary group. The differences in viability, progressive motility, and the percentage of moribund spermatozoa were statistically significant ($P<.05$), underscoring the positive impact of physical activity on semen quality (48). Gaskins et al. (49) built on this work by exploring the relationship between different types of activities and semen quality in a cohort of 189 young males. Their findings revealed that men in the highest quartile of moderate-to-vigorous activity had a 73% higher sperm concentration than those in the lowest quartile. In contrast, those watching over 20 hours of television weekly experienced a 44% reduction in sperm concentration (95% CI, 15%–63%). This study suggests that although moderate-to-vigorous physical activity may enhance sperm concentration, excessive sedentary behavior, such as prolonged television watching, could be detrimental (49).

Hajizadeh Maleki et al. (50) conducted a study involving 280 healthy male volunteers, aiming to discern the effects of varying exercise modalities on male reproductive markers. They found that moderate-intensity continuous training significantly ameliorated the markers of oxidative stress and inflammation in semen samples. In stark contrast, the other two modalities—strength training and high-intensity

interval training—did not yield similar improvements (50). In another study by Maleki et al. (51) focusing on men with infertility, participants underwent high-intensity exercise training. The results indicated significant reductions in inflammatory biomarkers and oxidative stress. Correspondingly, there were improvements in semen parameters and sperm DNA integrity, culminating in a higher pregnancy rate (51). Despite the prevailing evidence, Mínguez-Alarcón et al. (52) presented findings that deviated from the consensus. Surveying 215 men from a fertility clinic, their study did not identify a significant relationship between overall physical activity and semen quality. However, a noteworthy observation was the positive correlation between outdoor activities and an increased percentage of normal sperm morphology (52).

To summarize, the relationship between physical activity and semen parameters is intricate, with various studies shedding light on different facets. Although many of the studies underscore the positive implications of physical activity on male reproductive health, it is evident that the type and intensity of the activity play decisive roles. As research in this domain continues, a more thorough understanding will emerge and inform appropriate guidelines for the impact of physical activity on male reproductive health.

Impact of Weight Loss Medication on Semen Parameters

Four articles were identified that investigated weight loss medication and semen parameters. Metformin, primarily recognized for its role in diabetes management, has been linked to potentially deleterious effects on male fertility. Recent literature suggests that metformin adversely influences sperm motility, count, and overall quality. Raghif et al. (53) investigated 18 obese individuals diagnosed with idiopathic asthenozoospermia who were treated with metformin 850 mg twice daily for a duration of 12 weeks. There was a significant decrease in sperm count and motility after the treatment ($P<.001$). Contrarily, Zaidi et al. (54) presented a comparative study involving 50 insulin-dependent and 50 metformin-using individuals with DM. This study discerned an enhanced total sperm count in insulin-dependent individuals with DM, whereas metformin users showcased better sperm motility and morphology. Further evidence is limited, and the exact mechanisms are not fully understood but may involve testosterone, oxidative stress, and DNA integrity.

Since their approval for a clinical indication of weight loss, glucagon-like peptide 1 (GLP-1) agonist usage has increased and ushered in a new debate concerning their impact on semen parameters as a part of their side effect profile. Fontoura et al. (55) highlighted a unique case where a 35-year-old man exhibited deteriorated spermatogenesis after consuming 0.6-mg liraglutide daily. Intriguingly, on discontinuation, semen parameters normalized within a 5-month period, raising concerns regarding the medication's implications. On a broader spectrum, Andersen et al. (56) orchestrated a randomized, controlled, double-blind trial during encompassing 56 men. After an initial 8-week low-calorie diet, participants were randomized to various treatments, including liraglutide. The results conveyed that the initial weight loss positively influenced sperm concentration and count, which sustained over a year in those maintaining their weight loss. Conversely, endurance exercise extending over 60 weeks negatively impacted sperm concentration, motility, and morphology compared with moderate exercise.

As newer therapeutic options, GLP-1 agonists are gaining attention for their role in metabolic health and its effects on male fertility. The changes in semen parameters after the administration of weight loss medications likely stem from several different mechanisms. Preliminary hypotheses suggest that the negative impact of metformin could be linked to alterations in the testosterone levels, oxidative stress, and DNA integrity. Although the therapeutic benefits of weight loss medications, especially in the management of diabetes, are undeniable, their repercussions on male reproductive health remain a topic of contention. As research continues to investigate these implications, it is imperative to approach the use of these medications with an informed perspective, especially in the context of male fertility.

Impact of Gastric Bypass Surgery on Semen Parameters

The association of obesity with male reproductive dysfunction has led to a focus on the repercussions of surgical weight loss interventions, notably gastric bypass surgery, on male fertility. The available literature provides a broad perspective on the effects of such surgical interventions on semen parameters and reproductive hormones.

A consistent theme emerging from studies such as those of Legro et al. (57) and Wood et al. (58) is the improvement in the testosterone levels after gastric bypass surgery. Both studies observed a notable increase in the testosterone levels after the Roux-en-Y gastric bypass procedure. Legro et al. (57) documented significant increases in the urinary integrated total testosterone levels, starting from 3 months after surgery and persisting throughout the study duration. Similarly, Wood et al. (58) reported a substantial increase in the testosterone levels in obese males after surgery. This consensus underscores the potential of gastric bypass surgery to address hypogonadism, a frequent comorbidity in obese males (58).

Although the hormonal benefits are apparent, the literature paints a more complex picture regarding semen quality and sperm parameters postsurgery. Legro et al. (57) indicated that despite significant weight loss, semen parameters remained largely within typical ranges. Conversely, a meta-analysis by Wei et al. (59) flagged a decrease in sperm count and morphology, albeit with an observed increase in the semen volume after the surgery. This mixed trend was further highlighted by Samavat et al. (60), which documented improvements in the semen volume and viability ($P<.05$) but variability in sperm morphology. A more concerning observation came from Carette et al. (61), which highlighted a decrease in the total sperm count 1 year after surgery (−69.5 million, $P=.0021$). Similarly, Wood et al. (58) noted a reduction in the sperm concentration after the surgery, with certain patients even exhibiting azoospermia. This

potential adverse effect on sperm parameters was further emphasized in interesting case series by Razzaq et al. (62) and Miñambres et al. (63) that highlighted a decreased sperm count and morphology in 14 men.

In conclusion, although gastric bypass surgery undoubtedly offers hormonal benefits, particularly in increasing testosterone levels, its impact on semen parameters remains a topic of debate. The literature oscillates between reports of improved sperm parameters and potential detrimental effects, especially concerning sperm concentration and morphology. This dichotomy underscores the need for more comprehensive research, encompassing larger cohorts and extended follow-ups, to conclusively determine the implications of gastric bypass surgery on male fertility (Table 3).

CONCLUSION

Male factor infertility is an important issue, with evidence suggesting that both metabolic health and physical health significantly influence fecundity. The incidence rates of male obesity and metabolic diseases have been increasing for several decades, with 40% of males in reproductive ages being considered obese (8). This systematic review was conducted to explore the intricate relationship between male obesity, metabolic health, and fertility. Evidence strongly suggests that both obesity and metabolic disorders, such as diabetes and metabolic syndrome, have a negative impact on various parameters of male fertility, from semen quality to sperm DNA integrity and even ART outcomes. However, lifestyle interventions, such as physical exercise, generally appear to improve male fertility markers, although the type and intensity of exercise may play a crucial role. Pharmacologic treatments for weight loss, such as metformin and GLP-1 agonists, present a more complex picture, with studies suggesting both beneficial and detrimental effects on male reproductive health. Similarly, surgical interventions, such as gastric bypass surgery, show promise in improving hormonal imbalances but have mixed effects on semen parameters. As the incidence rates of obesity and metabolic disorders continue to increase, understanding these relationships becomes increasingly critical. The evidence calls for an approach to managing male fertility issues that contextualizes obesity and metabolic health. Future research, ideally encompassing larger samples and longer follow-up periods, is essential for clarifying these associations and informing clinical guidelines. In the interim, health practitioners should incorporate these insights into clinical practices, encouraging proactive lifestyle changes and providing targeted treatments to improve male reproductive health.

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