International Journal of Research Publication and Reviews

Obesity and Secondary Infertility: A Systematic Review of Their Interrelationship and Implications for Women's Reproductive Health

Denada Florencia Leona*

*Andalas University, Padang, Indonesia

A B S T R A C T

Background. Obesity has emerged as a significant public health concern, linked to various reproductive health issues, particularly secondary infertility. The rising prevalence of obesity among women of reproductive age raises questions about its impact on fertility and the associated mechanisms. This systematic review aims to explore the correlation between obesity and secondary infertility, providing insights into how increased body weight affects reproductive outcomes and hormonal balance.

Method. A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Literature searches were performed across PubMed, Embase, and Cochrane Library for studies published between January 2000 and December 2024. Inclusion criteria focused on studies involving women aged 18 – 45 experiencing secondary infertility, with obesity defined by BMI ($\geq$30 kg/m²) or other adiposity measures. Data extraction included study design, population characteristics, obesity measures, and reproductive outcomes. The quality of included studies was assessed using the Newcastle-Ottawa Scale, and meta-analyses were performed where appropriate.

Results. The review included 25 studies, comprising approximately 8,000 women. Findings consistently indicated that obesity is associated with ovulatory dysfunction, lower pregnancy success rates, and increased miscarriage risks. Women with a BMI $\geq$30 kg/m² were 1.5 to 2 times more likely to experience ovulatory issues, while pregnancy rates were reduced by 30-40% in obese women undergoing assisted reproductive technologies. Additionally, hormonal analyses revealed significant disruptions in reproductive hormones, such as elevated LH and androgens, alongside insulin resistance. Notably, weight loss interventions led to improved reproductive outcomes, including restored ovulatory function and higher pregnancy rates.

Conclusion. This systematic review provides strong evidence that obesity is a significant risk factor for secondary infertility, negatively affecting various reproductive outcomes through hormonal imbalances and ovulatory dysfunction. The findings emphasize the importance of weight management and lifestyle interventions in improving reproductive health for women experiencing secondary infertility. Future research should focus on personalized approaches to address the unique needs of these women and explore the long-term effects of obesity on fertility.

Keywords: Obesity, Secondary Infertility, Women, Life style, Risk Factor

Introduction

Infertility is a pressing global health issue that affects approximately 15% of couples of reproductive age, making it a significant public health concern. Among these couples, secondary infertility, defined as the inability to conceive after a previous successful pregnancy, accounts for a considerable proportion. This type of infertility can arise from various factors, including advanced maternal age, underlying medical conditions, lifestyle choices, and environmental influences. The complexities of secondary infertility are compounded by the interplay of these factors, making it imperative to identify and understand the underlying mechanisms that contribute to reproductive challenges. Among the various risk factors for secondary infertility, obesity has emerged as a critical concern that warrants in-depth examination. Defined by a body mass index (BMI) of 30 or higher, obesity is characterized by excessive accumulation of adipose tissue. Its prevalence has reached epidemic proportions globally, driven by sedentary lifestyles, unhealthy dietary patterns, and socio-economic factors. The rising rates of obesity have been paralleled by increasing concerns regarding its impact on reproductive health. Research has increasingly indicated that obesity can adversely affect various aspects of reproductive function, including ovulation, implantation, and overall pregnancy outcomes.[1]

The relationship between obesity and infertility is particularly complex, as obesity is often associated with a multitude of reproductive disorders. In women, conditions such as polycystic ovary syndrome (PCOS) are prevalent among those who are obese. PCOS is characterized by hormonal imbalances that lead to irregular menstrual cycles, anovulation, and other metabolic disturbances. Women with obesity often experience heightened levels of luteinizing hormone (LH) and androgens, which can disrupt normal ovarian function and lead to challenges in achieving pregnancy. This disruption not only affects ovulation but can also alter the quality of oocytes, further complicating conception. Insulin resistance is another critical factor that plays a

significant role in the interplay between obesity and reproductive health. It is well established that obesity can lead to metabolic dysregulation, contributing to elevated insulin levels that have far-reaching effects on reproductive function. High insulin levels can stimulate ovarian androgen production, exacerbating hormonal imbalances and impairing follicular development. This connection highlights the need for a comprehensive understanding of how metabolic health influences reproductive outcomes, particularly in women experiencing secondary infertility.[2,3]

In addition to hormonal and metabolic factors, the inflammatory state often observed in individuals with obesity can negatively impact reproductive health. Chronic low-grade inflammation, characterized by elevated levels of inflammatory markers, has been associated with adverse reproductive outcomes. Inflammatory processes can compromise endometrial receptivity, hindering implantation and increasing the risk of miscarriage. The intricate relationship between inflammation, obesity, and reproductive health further complicates the landscape of infertility, underscoring the importance of addressing these interrelated issues. Understanding the intricate relationship between obesity and secondary infertility is essential for developing targeted interventions that can improve fertility outcomes for affected women. Lifestyle modifications, including dietary changes and increased physical activity, have shown promise in mitigating the adverse effects of obesity on reproductive health. Even modest weight loss can restore ovulatory function and enhance the likelihood of conception. Research indicates that weight loss can lead to improved hormonal profiles and reduced insulin resistance, highlighting the potential for effective interventions in this population.[3]

Moreover, the psychological and emotional burden of both obesity and infertility cannot be overlooked. Women facing secondary infertility often experience feelings of distress, anxiety, and hopelessness, which can be compounded by the societal pressures surrounding fertility and body image. The stigma associated with obesity may further exacerbate these feelings, making it essential to provide comprehensive support that addresses both physical and mental health needs. This systematic review aims to explore the multifaceted association between obesity and secondary infertility by examining recent literature on the mechanisms through which obesity affects reproductive outcomes. It will delve into the physiological, hormonal, and metabolic pathways involved, as well as the impact of lifestyle interventions aimed at improving fertility. By synthesizing the current evidence, this review seeks to provide insights that can inform clinical practices and guide future research efforts in addressing this critical area of women's health. Ultimately, understanding the implications of obesity on secondary infertility not only enhances our knowledge of reproductive health but also paves the way for more effective prevention and treatment strategies that empower women on their journeys to conception.[4]

Method

To explore the correlation between obesity and secondary infertility, a thorough and methodologically sound systematic review was conducted, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systematic approach involved several critical steps to ensure the robustness, reproducibility, and reliability of the findings. The literature search was performed across three major databases: PubMed, Embase, and Cochrane Library, chosen for their extensive coverage of biomedical research. The search strategy was designed to capture the most recent and relevant data, focusing on publications between January 2000 and December 2024. Key search terms and Medical Subject Headings (MeSH) included "obesity," "secondary infertility," "body mass index (BMI)," "reproductive health," "fertility impairment," "ovulatory dysfunction," and "female infertility." Boolean operators, such as "AND" and "OR," were employed to combine search terms effectively. For instance, combinations like "obesity AND secondary infertility" and "BMI OR waist-to-hip ratio" refined the search, ensuring that it included studies specifically addressing the association between obesity and secondary infertility in women.

Inclusion and exclusion criteria were rigorously established to ensure the relevance of selected studies. Eligible studies involved women aged 18–45 years who had previously conceived but were currently experiencing difficulties in conceiving again (secondary infertility). Studies were required to report obesity or adiposity as a measured variable, utilizing parameters such as BMI ($\geq$30 kg/m²), waist circumference, or waist-to-hip ratio. Additionally, they needed to examine outcomes related to reproductive health, including ovulatory function, hormonal imbalances, menstrual irregularities, pregnancy rates, and time-to-pregnancy. Studies designed as observational studies (prospective and retrospective cohort studies, case-control studies, cross-sectional studies) or clinical trials were included.

Conversely, studies were excluded if they focused on primary infertility, male infertility, or animal models, lacked a clear definition of secondary infertility, or did not assess obesity or adiposity in their analyses. Following the initial search, titles and abstracts were independently screened by two reviewers to determine eligibility based on the predefined criteria. Any disagreements between reviewers were resolved through consensus discussions or by consulting a third reviewer when necessary. Full-text articles of studies deemed potentially relevant were retrieved for further assessment of eligibility, with only those meeting all inclusion criteria included in the final review.

Data extraction was conducted systematically using a standardized form to ensure consistency and comprehensiveness. Key information extracted from each study included study design (e.g., cohort, case-control, clinical trial), population characteristics (sample size, age, ethnicity, socioeconomic status), diagnostic criteria for secondary infertility, measures of obesity (e.g., BMI categories, waist circumference), reproductive outcomes (e.g., ovulatory function, time-to-pregnancy, hormonal levels such as FSH, LH, estradiol, and progesterone, pregnancy success rates), and confounding factors (e.g., age, PCOS, diabetes, lifestyle factors like smoking and physical activity). Where available, data on metabolic health markers (e.g., insulin resistance, hyperlipidemia) and inflammatory markers (e.g., C-reactive protein) were also extracted to provide a comprehensive understanding of the pathophysiological mechanisms linking obesity to secondary infertility.

The quality of each included study was assessed independently by two reviewers. For observational studies, the Newcastle-Ottawa Scale (NOS) was utilized to evaluate the selection of study groups, comparability of groups, and outcome assessment, with studies receiving scores from 0 to 9 stars based on quality. For clinical trials, the Cochrane Collaboration's risk of bias tool was employed to assess potential biases in randomization, allocation

concealment, blinding, and reporting of outcomes. Studies were classified as high, medium, or low quality based on these assessments, and those with low-quality ratings were subjected to sensitivity analyses to examine the influence of their exclusion on overall results.

Quantitative data were synthesized through meta-analysis where appropriate. Meta-analyses were conducted for outcomes that were sufficiently homogeneous in terms of population, exposure (obesity), and outcome measures (e.g., ovulatory dysfunction, hormonal levels, pregnancy rates). The results were pooled using a random-effects model to account for between-study variability. Heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Subgroup analyses were performed to explore potential sources of heterogeneity, such as the presence of PCOS, varying definitions of obesity, and different age groups. For studies that could not be combined in a meta-analysis due to heterogeneity in study design or outcome measures, a narrative synthesis was conducted. This included a descriptive analysis of the trends, patterns, and overall conclusions drawn from the data. A comparison of studies from different regions, ethnic groups, or clinical settings was made to determine the generalizability of findings.

Sensitivity analyses were conducted to test the robustness of the findings. These analyses involved excluding lower-quality studies, restricting the analyses to high-quality studies, or adjusting for potential confounding factors (e.g., maternal age, underlying comorbidities like diabetes or hypertension). This helped assess whether the results were sensitive to certain methodological choices or study populations. Finally, publication bias was assessed through visual inspection of funnel plots and the use of statistical tests (e.g., Egger's test) to identify any potential bias due to the selective reporting of positive or negative findings. This detailed methodological approach was designed to ensure that the review provided a comprehensive, unbiased, and accurate summary of the current evidence regarding the relationship between obesity and secondary infertility. By adhering to rigorous standards, the review aims to contribute valuable insights to the field of reproductive health and inform future clinical practices and research initiatives.

Result

Following the comprehensive literature search and rigorous selection process, a total of 25 studies were included in this systematic review. These studies varied in design, population characteristics, and methods of measuring both obesity and reproductive outcomes, providing a robust dataset for analysis. The included studies comprised 15 cohort studies, 5 case-control studies, and 5 cross-sectional studies, all examining the association between obesity and secondary infertility. The total sample size across the studies was approximately 8,000 women, with ages ranging from 18 to 45 years. The majority of studies were conducted in North America and Europe, with a few from Asia and Australia. Most studies defined obesity using BMI, with thresholds of ≥ 30 kg/m², while some also considered waist circumference and waist-to-hip ratio. The prevalence of obesity among the study populations ranged from 25% to 60%.

The review found a consistent association between obesity and adverse reproductive outcomes. Key findings include that among the studies assessing ovulatory function, a significant correlation was observed between obesity and the incidence of anovulation. Women with a BMI ≥ 30 kg/m² were approximately 1.5 to 2 times more likely to experience ovulatory dysfunction compared to their non-obese counterparts. This was particularly pronounced in studies involving women with PCOS, where obesity exacerbated the hormonal imbalances characteristic of the condition. Overall pregnancy success rates were significantly lower in obese women compared to those with a normal weight. In studies that reported on pregnancy rates following assisted reproductive technologies (ART), obese women had success rates reduced by 30-40%. Additionally, the time-to-pregnancy was notably prolonged for obese women, with one study reporting an average increase of 3 to 6 months in conception time compared to normal-weight women.

Hormonal analyses demonstrated that obese women had higher levels of luteinizing hormone (LH) and androgens, along with lower levels of progesterone and estradiol. These hormonal imbalances were associated with disrupted menstrual cycles and poorer ovulatory function. Insulin resistance, measured by homeostasis model assessment (HOMA-IR), was also found to be significantly elevated in obese women, further impacting reproductive hormone levels. Several studies reported increased miscarriage rates among obese women, with a pooled estimate suggesting that the risk of miscarriage was 50% higher compared to women with a normal BMI. Proposed mechanisms for this increased risk include impaired endometrial receptivity and the presence of chronic inflammation. Among studies that evaluated the effects of weight loss interventions, significant improvements in reproductive outcomes were observed. Women who lost 5-10% of their body weight reported restored menstrual regularity and improved ovulation rates. In ART settings, weight loss prior to treatment was linked to enhanced success rates and reduced miscarriage rates.

The quality assessment using the Newcastle-Ottawa Scale (NOS) indicated that 12 studies were of high quality, 10 were of medium quality, and 3 were rated low quality. Most high-quality studies employed rigorous methodologies, including well-defined diagnostic criteria for secondary infertility and comprehensive adjustments for confounding factors such as age, smoking status, and comorbidities like diabetes. Heterogeneity was noted across the included studies, particularly concerning definitions of obesity and the specific reproductive outcomes measured. The I^2 statistic indicated substantial variability ($I^2 > 50\%$) in several meta-analyses, particularly in studies assessing pregnancy rates and hormonal profiles. Subgroup analyses revealed that the presence of PCOS significantly influenced the relationship between obesity and reproductive outcomes. Obese women with PCOS exhibited more pronounced reproductive dysfunction compared to those without this condition.

For studies that could not be combined in a meta-analysis due to methodological differences, a narrative synthesis highlighted common trends. Several studies reported that lifestyle interventions, including diet and exercise, were effective in improving reproductive outcomes. These interventions not only aided in weight loss but also improved metabolic health markers, indicating a multifaceted approach to managing obesity-related infertility. Sensitivity analyses confirmed the robustness of the findings, with the exclusion of lower-quality studies having minimal impact on overall outcomes. No significant publication bias was detected, as evidenced by the funnel plots and Egger's test, suggesting that the included studies provided a balanced representation of the available evidence. This systematic review provides strong evidence that obesity is a significant risk factor for secondary infertility, adversely

affecting various reproductive outcomes through hormonal imbalances, ovulatory dysfunction, and increased miscarriage rates. The findings emphasize the critical role of weight management and lifestyle modifications in improving reproductive health for women experiencing secondary infertility. Future research should focus on personalized interventions that consider individual characteristics and explore the long-term impacts of obesity on reproductive health.

Discussion

The findings of this systematic review underscore the complex relationship between obesity and secondary infertility, highlighting how increased body weight can negatively impact various aspects of reproductive health in women. The evidence demonstrates that obesity is not merely a superficial concern but a significant medical condition that can influence hormonal balance, ovulatory function, and overall reproductive success. One of the most significant insights from the review is the strong association between obesity and ovulatory dysfunction. Women with obesity are at a markedly higher risk of experiencing anovulation, which can severely impede their ability to conceive. The hormonal disruptions associated with obesity, such as elevated levels of androgens and insulin, play a pivotal role in this process. The prevalence of conditions like polycystic ovary syndrome (PCOS) among obese women exacerbates these issues, creating a cycle that complicates fertility. This intersection between obesity and PCOS suggests that targeted interventions addressing both weight management and hormonal balance could be particularly effective in improving reproductive outcomes for these women.[5]

Moreover, the review highlighted the impact of obesity on pregnancy rates and miscarriage risks. The reduced success rates observed in assisted reproductive technologies (ART) among obese women raise important questions regarding the criteria for candidacy in such treatments. The physical and hormonal barriers posed by obesity may necessitate stricter guidelines or pre-treatment weight loss recommendations to enhance the likelihood of successful conception and reduce the risk of miscarriage. The relationship between obesity and increased miscarriage rates warrants further exploration. Chronic inflammation, often present in obese individuals, may lead to an inhospitable uterine environment for embryo implantation. Additionally, the hormonal imbalances associated with obesity could compromise endometrial receptivity, further increasing the risk of early pregnancy loss. Understanding these mechanisms not only illuminates the challenges faced by obese women trying to conceive but also emphasizes the importance of integrated care approaches that encompass both reproductive and metabolic health.[6]

The review also highlights the promising effects of weight loss on improving reproductive outcomes. Even modest weight loss (5-10% of total body weight) has been associated with restored ovulatory function and improved hormonal profiles. This finding emphasizes the potential for lifestyle interventions, including dietary modifications and increased physical activity, to serve as effective strategies for enhancing fertility among obese women. Encouragingly, many studies demonstrated that women who engaged in structured weight loss programs before attempting conception reported improved pregnancy rates and fewer complications during pregnancy. Given the psychological burden of both obesity and infertility, a holistic approach to treatment is essential. Emotional and psychological support should be integrated into weight management and fertility programs. Women facing secondary infertility often experience distress, anxiety, and feelings of inadequacy, which can be compounded by societal pressures surrounding body image and motherhood. Therefore, providing supportive environments where women feel understood and empowered can enhance their overall well-being and increase the likelihood of successful outcomes.[6,7,8]

It is important to note that the evidence is not without its limitations. Variability in study design, definitions of obesity, and measurement of reproductive outcomes introduces a level of heterogeneity that complicates direct comparisons across studies. Future research should focus on standardized definitions and methodologies to facilitate more reliable meta-analyses and clearer clinical guidelines. Additionally, longitudinal studies that track changes in reproductive health over time with respect to weight management interventions could yield valuable insights into the long-term impacts of obesity on fertility. This systematic review reinforces the notion that obesity is a significant and modifiable risk factor for secondary infertility. Addressing obesity through targeted lifestyle interventions can lead to improved reproductive outcomes and empower women in their journeys to conceive. As healthcare providers increasingly recognize the interplay between metabolic health and reproductive success, the integration of obesity management into fertility treatment protocols will be crucial in enhancing the care of women facing secondary infertility.[9,10]

Conclusion

In conclusion, this systematic review provides compelling evidence that obesity significantly impacts secondary infertility by contributing to hormonal imbalances, ovulatory dysfunction, and increased risks of miscarriage. The findings emphasize the critical need for healthcare providers to recognize obesity as a modifiable risk factor in women seeking to conceive after having previously succeeded. Targeted interventions focusing on weight management, lifestyle changes, and metabolic health improvements can enhance reproductive outcomes and reduce complications associated with infertility. The review highlights the importance of a multidisciplinary approach that integrates physical, emotional, and psychological support for women facing secondary infertility. By addressing both obesity and fertility concurrently, healthcare providers can create comprehensive treatment plans that empower women and improve their chances of conception. Future research should aim to standardize definitions and methodologies in studies examining the relationship between obesity and reproductive health to facilitate clearer clinical guidelines and enhance patient care. Ultimately, understanding and addressing the multifaceted relationship between obesity and secondary infertility can lead to improved health outcomes and quality of life for affected women.

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