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Impact of Obesity on Female Fertility

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Abstract:

Obesity and overweight are common conditions that have consequences not only on general health but also to a great extent on reproductive health. There is a high prevalence of obese women in the infertile population and numerous studies have highlighted the link between obesity and infertility. Obesity contributes to anovulation and menstrual irregularities, reduced conception rate and a reduced response to fertility treatment. It also increases miscarriage and contributes to maternal and perinatal complication. Reduction of obesity, particularly abdominal obesity, is associated with improvements in reproductive functions.

Introduction:

Obesity is a medical condition that occurs when a person carries excess weight or body fat. Doctors will suggest that a person has obesity if they have a high body mass index (BMI) see Table 1.

Obesity negatively impacts the health of women in many ways. Being overweight or obese increases the relative risk of diabetes and coronary artery diseases in females. Women who are obese have a higher risk of low back pain and knee osteoarthritis. Moreover, obesity negatively affects fertility as demonstrated by several experiments.

Infertility is a condition that affects approximately 1 out of every 6 couples. Infertility diagnosis is given to couples that have been unsuccessful in efforts to conceive over the course of one full year. When the cause of infertility exists within the female partner, it is referred to as female infertility.

The most common causes of female infertility include problems with ovulation, damage to fallopian tubes or uterus, or problems with the cervix. In addition, to that age can contribute to infertility because as a woman ages, her fertility naturally tends to decrease.

Obesity is associated with an increase in circulating insulin levels, which results in increasing functional androgen levels (caused by suppression of sex hormone–binding globulin synthesis and increased ovarian androgen production). Chronic elevation of circulating estrogen is caused by aromatization in peripheral adipose tissue. Additionally, leptin inhibits ovarian follicular development and steroidogenesis and thus may contribute to reproduction difficulties in obese women.

Table 1. Classification of overweight in adults according to BMI.		
Classification	**BMI (kg/m^2)**	**Risk of comorbidities**
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal	18.5–24.9	Average
Overweight	≥ 25	
Pre-obese	25–29.9	Increased
Obese class I	30–34.9	Moderate
Obese class II	35–39.9	Severe
Obese class III	≥ 40	Very severe

Aim of the Study:

The aim of this report is to illustrate the relation between obesity and female infertility.

Materials and Methods:

The Childhood Determinants of Adult Health (CDAH) study is a follow-up of 8,498 children, which included 4,191 girls who participated in the 1985 Australian Schools Health and Fitness Survey, a nationally representative sample of Australian school children aged 7–15 years , all children had physical assessments and those aged 9–15 years completed questionnaires. During 2002-2004, 3,412 women participants were traced and 2,734 women agreed to participate in the CDAH study (Fig. 1). During 2004-2006, when the participants were aged 26–36 years, 1,596 women completed questions on reproductive health (CDAH-1). The second follow-up (CDAH-2) was conducted during 2009-2011, when participants were aged 31–41 years and 1,129 women completed questions on reproductive health. After combining the two follow-ups, a total of 1,754 women who answered reproductive health questions at CDAH-1 or CDAH-2 or both were eligible for the study. The study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee. Written informed consent was obtained at both time points. Adult BMI was categorized into three groups (<25,25–30, and ≥30 kg/m2). Overweight was defined as 25 kg/m2 % BMI % 29.9 kg/m2 and obesity was defined as BMI ≥30 kg/m2

Adult Infertility Measurement

In the reproductive questionnaire of CDAH-1 and CDAH-2, women were asked to answer yes or no to questions ''Have you ever tried to become pregnant for 12 months or more without succeeding?'' and ''Have you ever seen a doctor because you were having trouble becoming pregnant?'' Infertility was recorded if they responded ''yes'' to either of the two questions. Women were further asked whether any of the following investigations had been undertaken if they reported having seen a doctor because of difficulty conceiving: hormone test, laparoscopy, and partner's semen test. Participants were also asked about any diagnosis they had been given including ovulatory problem, tubal problem, male factor,

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unexplained fertility problem, or any other female problem with a written specified reason see figure 1.

PubMed was used to collect all articles and studies used in this report. All graphs are plotted by using Microsoft Excel 2016. The used keywords are obesity , infertility , BMI [4] .

Figure 1: summarizes all steps in materials and methods

Results:

For consistently normal weight participants (normal weight in childhood and adulthood), the prevalence of infertility was 21.6%, and for consistently overweight/ obese participants (overweight/obese from childhood to adulthood), the corresponding figure was 27.9%. Although a higher prevalence of reported infertility was observed in the persistently overweight and obese group, the risk of infertility was significantly higher in women who were persistently overweight or obese from childhood (ages 7–11 years) into adulthood than those who had consistently healthy weight [4].
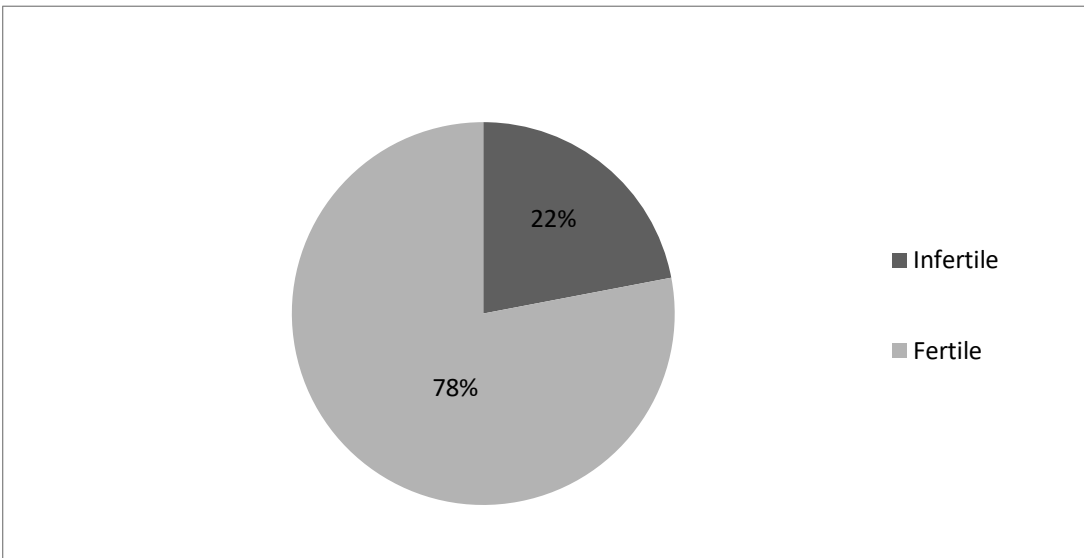

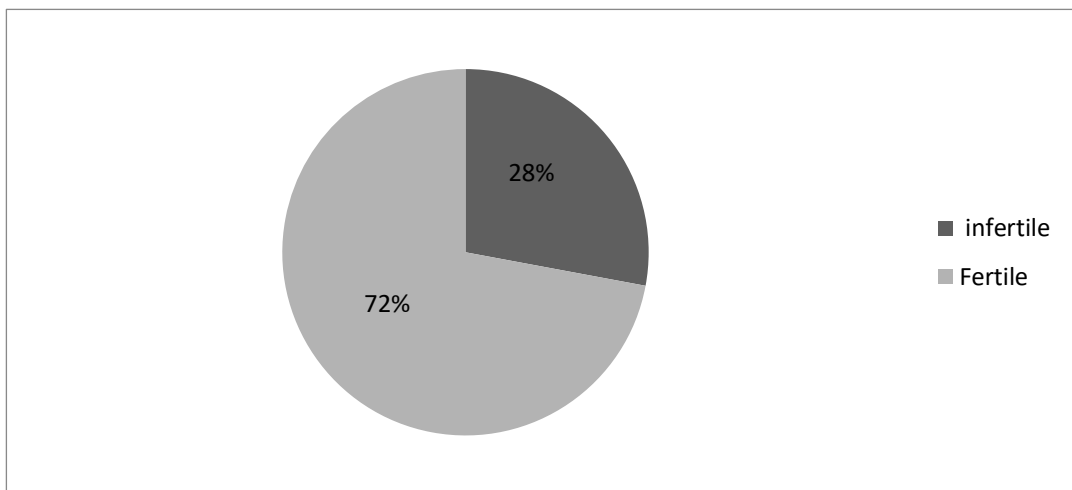**Figure 2**: Prevalance of Infertility in Normal Weight Participants

Figure 3: Prevalance of Infertility in Obese Participants

Discussion:

The link between obesity and infertility is complex. The available knowledge supports the concept that androgen alterations and their balance with estrogen represent the most important mechanism responsible for the development of subfertility or infertility in obese women. Sex hormone binding globulin (SHBG) is a protein carrier that binds testosterone and dihydrotestosterone with high affinity and estrogens with a lower affinity. The degree of obesity is inversely related to SHBG levels. In addition, body fat distribution further influences SHBG concentrations. Females with central adiposity have lower SHBG concentrations in comparison with peripheral obesity therefore the percentage of free testosterone fraction tends to be higher in women with central obesity. In addition, the adipose tissue is a site of active androgen production, converting androgens into estrogens, and of androgen and estrogen inter-conversion, which largely depends on the amount of fat. Increased androgen production and reduced binding of androgens to SHBG contribute to hyperandrogenism, resulting in anovulation through inhibition of follicular maturation [2].

Obese women often have higher circulating levels of insulin, which is a known stimulus for increased ovarian androgen production .These androgens are aromatized to estrogen at high rates in the periphery owing to excess adipose tissue, leading to negative feedback on the HPO axis (The hypothalamic–pituitary–gonadal axis (HPG axis) refers to the hypothalamus, pituitary gland, and gonadal glands as if these individual endocrine glands were a single entity . Gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus by GnRH-expressing neurons. The anterior portion of the pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the gonads produce estrogen and testosterone) and affecting gonadotropin production .This manifests as menstrual abnormalities and Ovulatory dysfunction [3].

In addition to insulin, any alteration in diet and/or weight may induce abnormalities in timing of sexual maturation and fertility. However, the cellular mechanisms involved in the fine coordination of energy balance and reproduction are largely unknown. The brain and hypothalamic structures receive endocrine and/or metabolic signals providing

information on the nutritional status and the degree of fat stores. Adipose tissue acts both as a store of energy and as an active endocrine organ, secreting a large number of biologically important molecules termed adipokines. Adipokines have been shown to be involved in regulation of the reproductive functions. The first adipokine described was leptin. Extensive research over the last 10 years has shown that leptin is not only an adipose tissue-derived messenger of the amount of energy stores to the brain, but also a crucial hormone/cytokine for a number of diverse physiological processes, such as inflammation, angiogenesis, hematopoiesis, immune function, and most importantly, reproduction. Leptin plays an integral role in the normal physiology of the reproductive system with complex interactions at all levels of the hypothalamic-pituitary gonadal (HPG) axis.

leptin augments secretion of gonadotropin hormones, which are essential for initiation and maintenance of normal reproductive function, by acting centrally at the hypothalamus to regulate GnRH neuronal activity and secretion, as well as acting directly on gonadotropes.

Not only does leptin participate in the control of gonadotropin secretion via its hypothalamic/pituitary actions, but circulating or locally produced leptin may also provide direct modulation of ovarian function. Leptin protein has been found in follicular fluid, with concentrations corresponding to those reported in serum .Leptin plays a role in both follicular development, where leptin transcript has been detected at early follicular stages, whereas leptin protein appears only in mature follicles ., and subsequent luteal function [1].

Conclusion:

Obesity is a vital condition and the number of obese women is increasing. The prevalent women health condition associated with obesity is infertility. Several clinical studies have shown the risk of high BMI in infertility as it is believed that obesity levels increase insulin and androgen, especially testosterone which leads to infertility.

Future Work:

Future work is required to give better understanding about the link between obesity and female infertility. In addition to that, further studies are needed to find an effective method to prevent infertility in obese women.

References:

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