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٢٠٠٧

THE EFFECT OF OBESITY ON FEMALE FERTILITY

ESSAY

SUBMITTED FOR PARTIAL FULFILLMENT OF MASTER DEGREE IN OBSTETRICS &GYNECOLOGY

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ABSTRACT

Obesity**,** particularly the abdominal phenotype, is associated with several reproductive disturbances. Whereas mechanisms by which obesity affect fertility are complex and still not completely understood, an important role appears to be played by the presence of a condition of functional hyperandrogenism and hyperinsulinaemia, which accompanies the insulin-resistant state. In women with the polycystic ovary syndrome, abdominal obesity may be co-responsible for the development of hyperandrogenism and associated chronic an ovulation, through mechanisms primarily involving the insulin-mediated overstimulation of ovarian steroidogenesis and decreased sex hormone binding globulin blood concentrations.

By these mechanisms, obesity may also favor resistance to clomiphene and gonadotrophin-induced ovulation and reduce outcomes of IVF/ICSI procedures. Due to the beneficial effects of weight loss, lifestyle intervention programmes should represent the first-line approach in the treatment of infertile obese women. Insulin-sensitizing agents may add further benefits, particularly if administered in combination with hypocaloric dieting. Therefore, individualized pharmacological support, aimed at favoring weight loss and improving insulin resistance, should be widely extended in clinical practice in obese infertile patients. This may be beneficial even during pregnancy, thereby permitting favourable physiological delivery and healthy babies.

Key words:

Obesity, polycystic ovarian syndrome, insulin, reproduction, weight loss.

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ARABIC SUMMARY

LIST OF ABBREVATIONS

ACTH	: Adrenocorticotropic hormone.
ADAMTS-1	: A disintegrin and metalloproteinase with athrombospondin-like motif.
AgRP	: Agouti regulated protein .
AMPK	:AMP-activated protein kinase.
ART	: Assisted reproductive technology.
BBT	: Basal body temperature
BMI	: Body mass index .
BRESS	: Behavioral Risk Factor Surveillance System.
CAMP	: Cyclic Adenosine Mono Phosphate
CART	: Cocaine- and amphetamine regulated transcript.
CIGMA	:Continuous infusion of glucose with model assessment test.
DHEAS	: Dehydroepiandrosterone sulfate
EGF	:Epidermal Growth Factor.
FGF	: Fibroblast Growth Factor
FSH	:Follicle-stimulating hormone .
GH	:Growth Hormone
GnRH	:Gonadotrophin-releasing hormone .
HCG	:Human choriogonadotrophin.
HDL	:High-density lipid.
HMG	:Human Menopausal Gonadotrphins
HMGB1	:High Mobility Group Box 1
HSG	:Hysterosalpingography .
IGF	:Insulin-like growth factor.
IGFBP-1	:Insulin-like growth factor binding protein-1.
IL6:	: Interleukin-6.
IU	: International unit.
IVF/ET	: In vitro fertilization/Embryo transfer.
IVF/ICSI	: In vitro fertilization/ intra cytoplasm sperm injection.
KDa	:Kilodaltons.
Kg	:kilogram.
LH	: Luteinizing hormone.
LOD	: Laparoscopic ovarian drilling
MAPK	. Mitogen Activated Protein Kinase
ng/ml	: nanogram per millilitre
NIH	: National Institutes of Health
NPY	: neuropeptide-Y.
Ob gene	:Obesity gene.
OHSS	:Ovarian hyperstimulation syndrome.

17-OHP :17-hydroxyprogesterone.

PAI-1 : Plasminogen-activator-inhibitor-**1**
PCOS :Polycystic ovary syndrome.
PPAR :peroxisome proliferator-activated receptor.
PPARγ :peroxisome proliferator- activated receptor-γ
POMC : pro-opiomelanocortin
q.i.d :quater in dies.
RCT :Randomized controlled trial
SCMC :Sperm-cervical mucus contact.
SHBG :Sex hormone-binding globulin.
SGA :Small for gestational age .
STAT1 :Signal transducer and activator of transcription 1.
TNF :Tumor necrosis factor.
TNF-α :Tumors necrosis factor-α.
U.S. :United states.
vs :Versus.

Introduction

Overweight and obesity represent a rapidly growing threat to the health of populations in an increasing number of countries worldwide (**World Health Organization, 1997).**

Many dietary lifestyles and possibly ethnic factors may prove to be important in determining the magnitude of the complications associated with obesity. These include non-insulin-dependent diabetes mellitus, cardiovascular diseases, cancers, gastrointestinal diseases and arthritis. In addition, significant associations are seen in reproductive endocrinology between excess body fat (particularly abdominal obesity) and irregular menstrual cycles, reduced spontaneous and induced fertility, increased risk of miscarriage and hormone-sensitive carcinomas **(Pasquali and Casimirri, 1993**).

Distinct changes in circulating sex hormones appear to underlie these abnormalities. The association between alterations of the reproductive functions in women was recognized long ago. In an original description, obesity together with hirsutism and infertility represented one of the characteristics of the eponymous syndrome. **(Stein and Leventhal, 1934).**

Much later, others showed that 43% of women, affected by various menstrual disorders, infertility and recurrent miscarriages, were either overweight or obese ***(Rogers and Mitchell, 1952)***.

More recently, it was shown that the presence of anovulatory cycles, oligoamenorrhoea and hirsutism, either separately or in

association, were signifcantly higher in obese than in normal-weight women ***(Hartz et al., 1979).***

In addition, the same authors found that the incidence of obesity during puberty and early adolescence was greater in adult married women without children than in those having had one or multiple pregnancies, thus confirming the existence of a correlation between obesity and infertility. Similar findings have been reported by others (***Norman and Clark, 1998).***

The relationship between excess body fat and reproductive disturbances appears to be stronger for early-onset obesity, although this remains a controversial issue due ,largely, to the heterogeneity of overweight or obese pre-adolescent or adolescent populations investigated ***(Azziz, 1989).***

There are several epidemiological studies which suggest that changes in body weight and/or body composition are critical factors regulating pubertal development in young women ***(Fishman, 1985***).

The discovery of leptin provided a unique explanation in this complex circuit. Leptin is a main product of body fat and, at the same time, regulates the gonadotrophin surge which initiates the development of pubertal stages (***Farooqi et al., 1999***).

Leptin provides a unique feedback signaling system that transmits information regarding adipose tissue energy stores to the central nervous system. Disruption of this system, by impaired leptin production or leptin receptor function, causes excessive food intake, decreased energy expenditure and severe obesity (***Klien et al., 2000).***

Several studies have repeatedly reported that the onset of menarche generally occurs at a younger age in obese girls than in normal weight girls **(*Bruni et al., 1985*).**

Just as the onset of menarche is earlier in obese women, data also suggest that the onset of ovarian failure and increased production of FSH at menopause occurs several years earlier in obese than in normal-weight women (***Norman and Clark, 1998***).

In addition, data exist which indicate that the association with menstrual disorders may be more frequent in girls with onset of excess body weight during puberty than in those who were obese during infancy. These findings have been substantially confirmed in a large study which was performed in approximately 6000 women and showed that obesity in childhood and in the early twenties increased the risk of menstrual problems. It is therefore likely that overweight and obesity do contribute to a significant proportion of menstrual disorders in young women (***Lake et al., 1997***).

Although many multiparous women are obese, evidence exists that obesity may also affect fertility rates in women within the fertile age. In the Nurses' Health Study it was reported that the risk of ovulatory infertility increased in women with increasing body mass index (BMI) values (***Norman and Clark, 1998).***

Similarly, there are consistent data indicating that obesity is also associated with an increased risk of miscarriage (***Norman and Clark, 1998***).

In contrast, others**,** while examining a large group of nulliparous healthy women who presented for artificial insemination due to infertility

of their partners, found that body fat distribution rather than fat amount was associated with a decreasing chance of conception ***(Zaadstra et al., 1993***).

Therefore, due to the increasing world epidemic of obesity during the past decade; it is believed that much more updated investigations should be performed in order to evaluate whether this is associated with a parallel increase of adverse effects on fertility in women . Polycystic ovary syndrome(PCOS),one of the most common endocrine disorders, affects approximately six percent of women of reproductive age The syndrome may have an initial onset in the peripubertal years and is progressive ***(Hunter and Sterrett, 2000).***

Almost half of adult females with polycystic ovary syndrome are obese and many have a central distribution of body fat. This condtion frequently has its origin in adolescence. It is associated with increased androgen secretion, hirsutism, menstrual abnormalities and infertility, but these may not be present in every case (***Slyper, 1998***).

Metabolic disorders, such as the development of insulin resistance , result from the increasing incidence of obesity, and have serious ramifications on the progression of lifetime health problems such as type II diabetes, cardiovascular disease, dyslipidemia and hypertension. A significant proportion of the infertile or sub-fertile population are obese or overweight (***Crosignani et al., 2002***) with a plethora of reproductive complications including menstrual dysfunction and anovulation ***(Lake et al., 1997)*** and miscarriage ***(Wang et al., 2002).***

AIM OF THE WORK

This review focuses on increasing the awareness of disordered over-eating behaviors, causing overweight and obesity , and describes health risks associated with obesity and its impact on female reproduction. The concept of changing the life style towards a regular physical activity with a proper balanced diet should be settled in mind so that decrease the cardiovascular and endocrinal diseases and the reproductive functions are not impaired.

Chapter 1

OBESITY

Venus of willendorf-

OBESITY

Definition

Obesity is often defined simply as a condition of abnormal or excessive fat accumulation in adipose tissue to the extent that health may be impaired (***Garrow, 1988).***

In the clinical setting, obesity is typically evaluated by measuring BMI (body mass index), waist circumference, and evaluating the presence of risk factors and comorbidities.

BMI

BMI, or Body Mass Index, was developed by the Belgian anthropometrist Adolphe Quetelet. It is calculated by dividing the subject's weight in kilograms by the square of his/her height in metres (*BMI = kg / m^2*). The current definitions commonly in use establish the following values, agreed in 1997 and published in 2000 (***World Health Organization, 2000***).

A BMI less than 18.5 is *underweight*.

A BMI of 18.5 - 24.9 is *normal weight*.

A BMI of 25.0 - 29.9 is *overweight*.

A BMI of 30.0 - 39.9 is *obese* .

A BMI of 40.0 or higher is *severely (or morbidly) obese*.

BMI is a simple and widely used method for estimating body fat ***(Am J Clin Nutr, 2002***).