Chapter 6

Can Lifestyle Factors of Diabetes Mellitus Patients Affect Their Fertility?

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1. Introduction

An increase in the number of diabetics diagnosed at a young age has coincided with worldwide concerns over the fertility status of these individuals. Infertility is already a major health problem in both the developed and developing world, with up to one in six couples requiring specialist investigation or treatments in order to conceive (Agbaje et al., 2007). Diabetes mellitus (DM) has impacted directly and indirectly on the fertility of couples (Glenn et al., 2003). It may affect both male and female reproductive function at multiple levels as a result of its effects on the endocrine system as well as on vasculature (Sexton and Jarow, 1997).

In a report released by the World Health Organization (WHO, 2004) indicated that the worldwide prevalence of diabetes was estimated to be 2.8% in 2000; furthermore, it was predicted to increase to 4.4% by 2030. The total number of people with diabetes was projected to rise from 171 million in 2000 to 366 million in 2030. It was also evident that the prevalence of diabetes is higher in men than in women, but there are more women with diabetes than men as females tend to have an increased life expectancy. These findings indicate that the "diabetes epidemic" will continue (Wild et al., 2004).

When a person has diabetes or insulin resistance, it may generate a hormone imbalance which can trigger a domino-like effect with the remaining hormones, including estrogen, progesterone and testosterone levels. These hormone imbalances can cause a wide variety of side effects, ranging from ovarian cysts to ED and infertility. The neuroendocrine effects may potentiate the adverse effects of diabetes on other organ systems and, in the case of reproductive function, are often of major patient concern (Steger and Rabe, 1997).

A recent study (Agbaje et al., 2007) strongly suggests that DM impairs male fertility, and the rising rates of diabetes may well pose a significant problem to human fertility. Male infertility problems may become more widespread as diabetes rates rise. Already the

frequency of defective spermatogenesis and accompanying decreases in sperm parameters such as sperm count and motility appear to be on the increase. Arguably one of the most compelling reasons for this phenomenon is the contributing influence of environmental and lifestyle factors on male reproduction.

Lifestyle factors have had a dramatic impact on general health and the capacity to procreate. Cigarette smoking has been associated with adverse effects on fertility (Roth and Taylor, 2001). Poor diet and obesity are known to be key factors in the increase in Type 2 DM which has led to the increased risk for infertility. Despite the lack of conclusive studies, it is evident that there are enough compelling reasons to believe that the future of male and female fertility may be actively affected and impaired by DM, lifestyle and environmental factors.

In this review not only the effects of DM will be discussed, but also several lifestyle factors and occupational exposure that can impinge on the process of fertility. If and how lifestyle changes can positively impact on the diabetic patient's fertility status will also be investigated.

2. Lifestyle effects on fertility

Infertility is an increasingly prevalent issue; researchers point towards changing environmental and lifestyle conditions as arguably the most significant causes of this phenomenon. Environmental and lifestyle exposure to a wide variety of factors may stress the male reproductive system throughout a man's lifespan, from gestation to advanced adult age. Various environmental contaminants have been shown to impair sperm function through oxidative damage to sperm membranes. Reactive oxygen species (ROS)-mediated damage of sperm membranes has been reported to be responsible for impaired sperm motility (Archibong et al., 2008, de Lamirande and Gagnon, 1992). DNA damage, sperm head abnormalities (Kumar et al., 2002) as well as abnormal sperm function (Archibong et al., 2008) and impaired (?)sperm DNA integrity (Saleh et al., 2002) have been proven to be caused by the effects of environmental contaminants on the epididymis. Ultimately, male infertility may be the result of exposure to any combination of factors such as chemical toxins, smoking and alcohol abuse, poor diet and a lack of exercise and obesity, different types of stress, and the increasing prevalence of cellphone and ionizing radiation.

Despite the lack of conclusive studies tracking effects of the environment and lifestyle of an individual throughout life, there is enough reason to believe that the environment and lifestyle play significant roles in the quality of male gamete production and thus male fertility as a whole. This argument is supported by the fact that over the last 50 years mean sperm counts in the general population have decreased by 50% while dramatic environmental and lifestyle changes have occurred during this same period.

The prevalence of DM2 is increasing at a high rate, and the economic costs of caring for patients with diabetic complications are high. The increase in DM2 is closely associated with the epidemic of obesity in industrialized countries (Bruns and Kemnitz, 2004). Reduced physical activity is a contributing factor as sedentary lifestyles become more common.

Increased body fat, particularly in the visceral compartment, is a strong risk factor for the development of DM2. Elucidation of such risk factors will lead to interventions that can delay the onset or protect against the development of DM2 (Bruns and Kemnitz, 2004). Diabetes mellitus, whether due to lack of insulin secretion or resistance to insulin action, has adverse effects on all organ systems.

3. Brief overview of diabetes mellitus

Diabetes mellitus is a disorder in which blood levels of glucose are abnormally high because of the body's inability to release or to respond to insulin adequately. As the oxidation or metabolism of these sugars from carbohydrates is the major source of energy for the human body, diabetes can lead to major systemic problems.

Insulin, a hormone released from the pancreas, allows glucose to be transported into cells so that they can produce energy or store the glucose until it is needed. Scientists believe that an environmental factor (possibly a viral infection or a nutritional factor in childhood or early adulthood) could cause the immune system to destroy the insulin-producing cells in the pancreas. Some genetic predisposition is most likely needed for this to happen(Thorsby and Lie, 2005).

Whatever the cause, in Type 1 diabetes more than 90 percent of the insulin-producing beta cells of the pancreas are permanently destroyed. This results in severe insulin deficiency and approximately 10 percent of people with diabetes have Type 1 diabetes. Most people who have Type 1 diabetes develop the disease before the age of 30; and, in order to survive, a person with Type 1 diabetes must regularly inject him- or herself with insulin. In Type 2 diabetes mellitus (non-insulin-dependent diabetes), the pancreas continues to manufacture insulin, sometimes at even higher than normal levels. However, the body develops resistance to its effects, resulting in a relative insulin deficiency(Ferrannini, 1998).

Type 2 diabetes may occur in children and adolescents but usually begins after the age of 30 and becomes progressively more common with age: ninety percent of people with diabetes have Type 2 and about 15 percent of people over age 70 have Type 2 diabetes. Type 2 diabetes occurs when the pancreas does not produce enough insulin or when the body does not use the insulin that is produced effectively due to the development of insulin resistance(Ferrannini, 1998). DM2 is associated with a sedentary lifestyle and obesity. Obesity is a risk factor for Type 2 diabetes; 80 to 90 percent of the people with this disease are obese (Wild et al., 2004). Certain racial and cultural groups are at increased risk: Blacks and Hispanics have a twofold to threefold increased risk of developing Type 2 diabetes. Type 2 diabetes also tends to run in families.

Diabetes is one of the leading causes of death by non-communicable diseases worldwide. If not recognized or improperly managed, the high levels of blood glucose can slowly damage both the small and large blood vessels and the imbalance in hormones can impact negatively on the endocrine system. Not only does it result in many serious health complications such as heart disease, it is also a leading cause of adult blindness and kidney disease (Azadbakht et al.,

2003, Pradeepa et al., 2002). At least 50% of all limb amputations, not due to traumatic injury, are due to diabetes. Diabetes is now considered to be a major cause of erectile dysfunction and also recognized to impact severely on reproductive capacity (Azadbakht et al., 2003).

Type 1 and Type 2 diabetes are on the increase throughout the world, with the latter increasingly being described as a "modern disease" caused by lifestyle, diet and obesity. The reason for the increase in Type 1 diabetes is not known, but some scientists are suggesting that genetic factors could be involved, or that viruses could trigger the onset of the disease (Agbaje et al., 2007).

4. Neuroendocrine effects of diabetes mellitus

Diabetes mellitus in humans is often associated with hypofunction of the hypothalamic-pituitary-thyroid axis (HPTA) (Akbar et al., 2006, Hollowell et al., 2002, Papazafiropoulou et al., 2010, Radaideh et al., 2004). Stress, which is associated with diabetes, may also cause changes in the hypothalamus-anterior-pituitary axis in these diabetics. It appears that the presence of sub-clinical hypothyroidism and hyperthyroidism may result from hypothalamus-pituitary-thyroid-axis disorders (Celani et al., 1994). Several investigators have demonstrated that DM affects the function of the hypothalamus. Thyroid hormones affect glucose metabolism via several mechanisms. Hyperthyroidism has long been recognized to promote hyperglycemia (Maxon et al., 1975). During hyperthyroidism, the half-life of insulin is reduced, most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors (Dimitriadis et al., 1985, O'Meara et al., 1993). In addition, untreated hyperthyroidism was associated with a reduced C-peptide to pro-insulin ratio suggesting an underlying defect in pro-insulin processing (Beer et al., 1989). Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is the increase in the gut glucose absorption mediated by the excess thyroid hormones (Foss et al., 1990). When DM is accompanied by hyperthyroidism, it worsens hyperglycemia through several pathological conditions caused by excessive thyroid hormones, such as increased glucose absorption from the intestine, decreased insulin secretion, decreased peripheral glucose consumption due to insulin resistance, increased hepatic glucose production due to activated glucose metabolism such as gluconeogenesis or glycogenolysis, accelerated breakdown of triglyceride in adipose tissue, and augmented renal clearance of insulin (Bhattacharyya and Wiles, 1999, Foss et al., 1990). As for hypothyroidism, glucose metabolism is affected as well via several mechanisms. A reduced rate of liver glucose production is observed in hypothyroidism (Okajima and Ui, 1979) and accounts for the decrease in insulin requirement in the hypothyroid diabetic patient. Recurrent hypoglycemic episodes are the presenting signs for the development of hypothyroidism in patients with Type 1 diabetes and replacement with thyroid hormones reduces the fluctuations in blood glucose levels (Leong et al., 1999).

Men with Type 2 diabetes mellitus have a higher prevalence of low testosterone levels than age-matched controls. In numerous cross-sectional studies, levels of testosterone in men have been inversely associated with several recognized risk factors for the development of

Type 2 diabetes, such as obesity, central adiposity (belly fat), and an elevated fasting plasma concentration of insulin and glucose. Several prospective studies found that low levels of testosterone and sex hormone–binding globulin predict the subsequent development of Type 2 diabetes among aging men. Low plasma testosterone concentration is associated with other correlates of diabetes, such as cardiovascular disease and hypertension (Khaw et al., 2007).

These neuroendocrine effects may potentiate the adverse effects of diabetes on other organ systems and, in the case of reproductive function, is often of major patient concern.

5. Effects of diabetes mellitus on male fertility

It is estimated that 15% of couples attempting to conceive are not able to do so within one year. Male factor infertility is present in 20%–50% of these couples, either independently or in conjunction with female factor infertility issues (Jarow et al., 2002, Sigman, 1997). Diagnosis of male infertility includes a thorough physical examination, semen analysis, ultrasound, and hormonal tests, if warranted. Male infertility can result from a low sperm count, which means the testes have produced less sperm than normal. The sperm may also have been unable to exit the testes, or they might not be fully functional. Male infertility may also result from a number of factors including: underlying health conditions, retrograde ejaculation, environmental pollutants and lifestyle factors.

Certain diabetic complications can cause issues for men that contribute to infertility (Figure 1). As DM has profound effects on the neuroendocrine axis (Steger and Rabe, 1997), in men, both DM1 and DM2 have long been recognized as major risk factors for sexual and reproductive dysfunction. This primarily includes impotence/erectile dysfunction (ED), ejaculatory (retrograde ejaculation) and orgasmic problems, as well as low desire (reduced libido), but impaired spermatogenesisis is also associated with DM (Bartak et al., 1975, Bhasin et al., 2007, Brown et al., 2005, Fairburn, 1981, Kolodny et al., 1974).

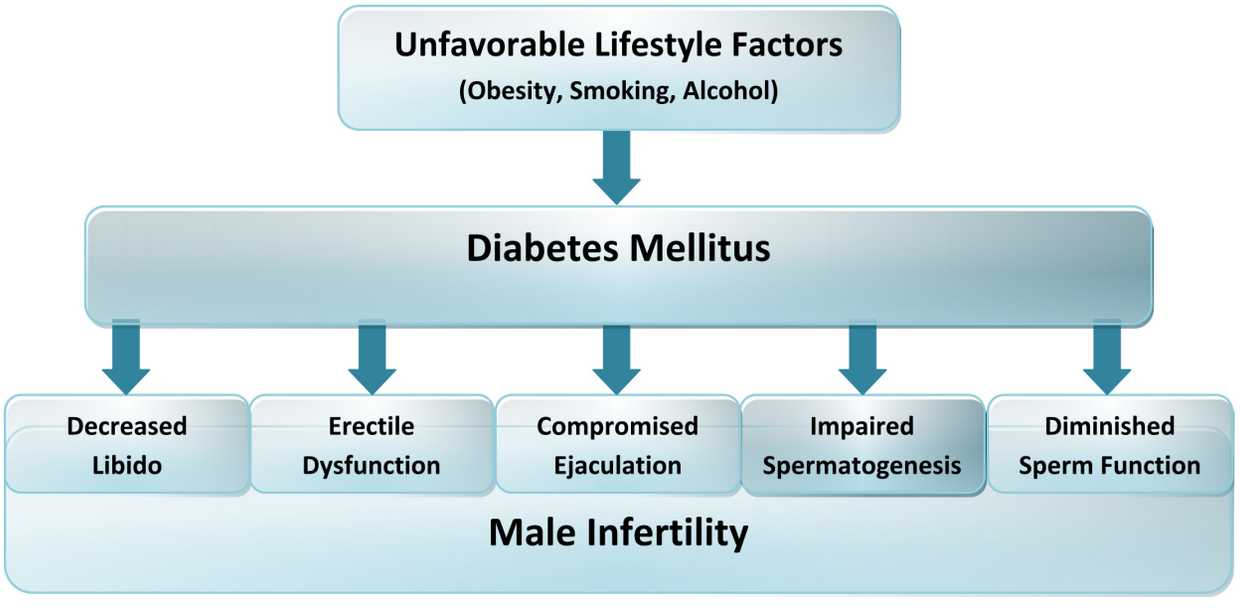

Figure 1. The possible effect of DM and accompanying unfavorable lifestyle choices on male fertility.

Nerve damage or autonomic neuropathy due to diabetes can lead to retrograde ejaculation – where the semen goes into the bladder. Since the semen never reaches the female reproductive system, infertility may be an issue.

The majority of patients with Type 2 diabetes are overweight or obese, which leads to decreased testosterone levels and elevated pro-inflammatory cytokines (substances produced in the cell). This can induce dysfunction in the blood vessel wall through the so-called nitric oxide pathway and further explain the relationship between DM2, obesity and erectile dysfunction(Bhasin et al., 2007, Brown et al., 2005).

Erectile dysfunction, or the inability to achieve an erection, is another diabetes complication that can lead to fertility problems in diabetic men (Brown et al., 2005, Lewis et al., 2004, Rosen et al., 2000). In men with DM, factors including aging, cardiovascular disease, high body mass index (BMI), hypercholesterolemia, smoking, and medication, in combination with DM-specific factors, such as duration and severity of DM and diabetic complications (neuropathy, nephropathy, retinopathy, and vascular damage), there is a strong correlation with ED (Brown et al., 2005, Lewis et al., 2004, Rosen et al., 2000). The mechanisms for ED in men with DM are endothelial dysfunction, dysfunction of the nitric oxide (NO) pathways (down regulation of NO synthase and degeneration of nitrergic nerves), dysfunction of other signal transduction pathways, corporal smooth muscle degeneration, and tissue remodeling (Brown et al., 2005, Saenz de Tejada et al., 1989). Sexual stimulation activates the non-adrenergic, noncholinergic nerve and activates the neural NO synthase⁄cGMP pathway. The release of NO facilitates the relaxation of penile cavernosal arteries and resistance arterioles, which causes vasodilation, and increases blood flow to the corpus cavernosum. The increased blood flow stimulates the endothelium lining of the lacunar spaces of the corpus cavernosum to release endothelial NO from the endothelium NO synthase. These biochemical and physiological processes result in trabecular smooth muscle relaxation and expansion of the sinusoids within the corpora cavernosa, leading to penile engorgement. This expansion of the corpora cavernosa against the tunica albuginea results in veno-occlusion and trapping of blood under pressure. This process is referred to as the 'veno-occlusive' mechanism. Neural and endothelial NO synthases are regulated by androgens. In addition, the tissue histo-architecture is dependent on androgens. Thus, any perturbations or alterations in the neural, vascular or erectile tissue fibroelastic properties will contribute to ED, by altering the veno-occlusion mechanism (Traish et al., 2009). Obesity essentially impinges on the male reproductive system and fertility through its effects on ED and impaired semen parameters. Several scholars have reported a correlation between obesity and ED. Corona et al. (2006) presented evidence showing that 96.5% of their subjects with metabolic syndrome (MetS), which is characteristic of abdominal obesity, exhibited ED (Corona et al., 2006). A direct proportional relationship between the increasing severity of obesity and the severity of ED was reported. In addition, there are reported relationships between low serum testosterone concentrations and ED in obese patients and those with MetS syndrome and Type 2 diabetes mellitus. They found negative correlations between BMI and self-reported satisfaction with erection as well as between BMI and the percentage of men reporting full erection.

As a consequence of insulin resistance in patients with Type 2 diabetes, high circulating levels of insulin are present in the bloodstream. Hyperinsulinemia, which often occurs in obese men, has an inhibitory effect on normal spermatogenesis and can be linked to decreased male fertility. In a group of diabetic men, apart from semen volume (2.6 vs. 3.3ml), semen parameters (concentration, motility and morphology) did not differ from those of the non-diabetic control group, but the amount of nuclear and mitochondrial DNA damage/fragmentation in the diabetic patients' sperm was significantly higher (52% versus 32%) (Agbaje et al., 2007). There were more deletions in the mitochondrial DNA of diabetic men's sperm cells than those of the non-diabetic men. The mitochondrial DNA deletions in the diabetic men's sperm cells ranged from 3 to 6 and averaged 4, while for the non-diabetic men it ranged from 1 to 4 and averaged 3. Deletions and fragmentation of DNA results in loss of genetic material which, in the case of nuclear DNA, causes infertility as the sperm is not able to deliver its full complement of genetic codes when fusing with the egg in order to create a viable embryo. The researchers concluded that diabetes is associated with increased sperm nuclear and mtDNA damage that may impair the reproductive capability of diabetic men.

In addition to inducing sperm DNA damage, insulin levels have also been shown to influence the levels of sex-hormone-binding globulin (SHBG), a glycoprotein that binds to sex hormones, specifically testosterone and estradiol, thereby inhibiting their biological activity as carriers. High circulating insulin levels inhibit SHBG synthesis in the liver, whereas weight loss has been shown to increase SHBG levels (Lima et al., 2000). In obese males, the decrease in SHBG means that less estrogen will be bound, resulting in more biologically active, free estrogen. In addition to the conversion of testosterone to estrogen in obese patients, the decreased ability of SHBG to sustain homeostatic levels of free testosterone also contributes to abnormal testosterone levels (Jensen et al., 2004). This failure to maintain homeostatic levels might magnify the negative feedback effect of elevated total estrogen levels. Even when the presence of SHBG is accounted for, an independent relationship between insulin resistance and testosterone production can still be demonstrated (Tsai et al., 2004). Therefore, the levels of SHBG might be important only as a marker of altered hormone profiles in obese infertile men. Reductions in semen volume and a higher mean incidence of nuclear DNA fragmentation is seen in diabetic men compared to those without Type 2 diabetes (Agbaje et al., 2007).

Male infertility may represent perturbation in some male patients with MetS,. Obesity is a cardinal feature of MetS. Adverse effects of obesity on male fertility are postulated to occur through several mechanisms. First, peripheral conversion of testosterone to estrogen in excess peripheral adipose tissue may lead to secondary hypogonadism through hypothalamic-pituitary-gonadal axis inhibition Kasturi et al., 2008). Second, oxidative stress at the level of the testicular microenvironment may result in decreased spermatogenesis and sperm damage. Lastly, obesity accompanying DM2 is often associated with decreased physical activity and increased fat deposition. The accumulation of fat in the suprapubic and inner thigh area as well as in the scrotum may result in increased scrotal and testicular temperatures in severely obese men (Kasturi et al., 2008). Increased testicular temperature also adversely affects sperm production Kasturi et al., 2008).

Du Plessis and colleagues (2010) report that an increase in the size or number of adipocytes as a result of obesity can result in both physical changes and hormonal changes. Physical changes can include an increase in scrotal temperature, an increase in the incidence of sleep apnea, and an increase in ED. Hormonal changes might include increases in the levels of leptin, estrogen and insulin, and a decrease in the level of testosterone. These changes, in turn, contribute to oligozoospermia, azoospermia, an increase in the DNA fragmentation index (DFi), and a decrease in semen volume. All three categories of change contribute to obesity-linked male infertility (Azadbakht et al., 2003, Du Plessis et al., 2010).

Du Plessis et al. (2010) propose that the dysregulation of the typical hypothalamic–pituitary–gonadal axis is a consequence of obesity. The increase in estrogen and decrease in testosterone levels negatively affects spermatogenesis as well as regular testicular function. Inhibin B levels are directly related to normal spermatogenesis and thus the low levels of this protein observed in obese males result in abnormal spermatogenesis. The dysregulation of the axis is shown because, despite the low inhibin B levels observed in obese males, there is no compensatory increase in follicle-stimulating hormone (FSH) levels as expected. Increased estrogen levels further contribute to the negative feedback effect on the hypothalamus and lead to decreased gonodoliberin and gonadotropin release (Du Plessis et al., 2010).

It is therefore clear that DM can be associated either directly or indirectly with several disorders of the male reproductive system and sexual functioning (Dinulovic and Radonjic, 1990).

6. Effects of diabetes mellitus on female fertility

Women reach their peak fertility age around their early 20s, but from approximately age 35 to 40, a woman is significantly less likely to fall pregnant. There are many factors that can lead to infertility. In order for a fertilized egg to grow successfully in the womb, it must be released by a woman's ovaries, implanted in the lining of the uterus and survive. Infertility may occur if initially, the ovaries have difficulty producing eggs.. These challenges to fertility can be caused by lifestyle habits or underlying health problems.

Hormonal disorders such as thyroid disease or abnormal hormone levels may also lead to infertility. Chronic diseases including autoimmune disorders, diabetes, cancer and endometriosis also make it more difficult to conceive, as can problems within or around the genital area, such as ovarian cysts or pelvic inflammatory disease. Eating disorders, poor nutrition, obesity and substance abuse may all contribute to infertility in both men and women.

Obesity and insulin resistance are two of the most common factors that lead to infertility, especially female infertility. More patients are diagnosed with Polycystic Ovarian Syndrome (PCOS) and Dysmetabolic Syndrome X, which affects about 25% of the population. A Swedish study, published in 2007, associated Type 1 diabetes with reduced fertility.

PCOS is the most common cause of female infertility (Cupisti et al., 2010). It is related to diabetes because of the strong feature of insulin resistance (inefficient insulin) in this subset of women. Many patients with PCOS have diabetes. PCOS is characterized by irregular or

absent menstrual periods, problems with ovulation, increased levels of androgens such as testosterone, and ovaries with multiple cysts (Lobo and Carmina, 2000, Pasquali et al., 2011).

In PCOS, too much testosterone is produced and this affects the ability of the eggs to mature within the ovaries. Because women with PCOS develop insulin resistance, there are often ovulatory problems leading to irregular periods. Because of the irregularity of their cycles, cysts develop, which are fluid-filled cavities within the ovaries. Over time all of these issues make the likelihood of pregnancy begin to seem more and more distant (Lobo and Carmina, 2000).

Anovulation (failure to ovulate) is the causeof about 25% of female infertility cases, with PCOS being the most common cause of anovulation (Cupisti et al., 2010, Goodarzi et al., 2011, Lobo and Carmina, 2000, Walters et al., 2012). This means that PCOS could be a factor in about one-fifth of all infertility cases.

Insulin is said to bind with low affinity to the luteinizing hormone receptor in the theca cells of the ovaries. The hyperinsulinemia or high insulin levels present in obesity, MetS, diabetes, or insulin resistance in general may stimulate ovarian theca cells and thus increase the production of hormones, including androgens. This, in turn, may inhibit normal ovulation because of the hampered development of ovarian follicles. In women with PCOS, immature follicles bunch together to form large clumps. The eggs may mature within the bunched follicles, but the follicles do not break open to release them. Thus, women with PCOS often do not have regular menstrual periods. Also, because the eggs are not released, most women with PCOS have difficulty falling pregnant (Goodarzi et al., 2011, Lobo and Carmina, 2000, Mellembakken et al., 2011, Pasquali et al., 2011, Walters et al., 2012).

There appears to be a higher rate of miscarriage in women with PCOS. Increased levels of luteinizing hormone, which aids in the secretion of progesterone, may play a role. Increased levels of insulin and glucose may cause problems with the development of the embryo. Insulin resistance and late ovulation (after day 16 of the menstrual cycle) also may reduce egg quality, which can lead to miscarriage.

Insulin resistance is found in up to 60% of obese women and 40% of non-obese women. Of the people diagnosed with Type 2 diabetes, 80% to 90% are also diagnosed as obese. This fact provides an interesting clue to the link between diabetes and obesity. The main diabetes complication (including gestational diabetes) related to pregnancy is macrosomia - or a big baby (higher than the 90th percentile in birth weight). Sometimes these babies are not able to pass through the birth canal, so there are higher incidences of caesarean sections, and sometimes it is necessary to induce labor early. Fetal distress can also become an issue. There is also an increased risk of birth defects. This condition is directly related to maternal diabetes problems, especially during the first few weeks when a woman may be unaware she is pregnant. For this reason, women with diabetes are advised to manage their insulin levels under control before attempting to conceive.

Conditions associated with insulin resistance, such as obesity and DM, are often accompanied by increased adiposity or hyperglycemia (Vega et al., 2006). Obesity and

diabetes are independently associated with altered female reproductive function (Kjaer et al., 1992, Pettigrew and Hamilton-Fairley, 1997, Zaadstra et al., 1993). Despite the fact that more women suffer from DM than men, and that women share similar risks for diabetic complications with men, less attention has been given to sexual function in women with DM. The prevalence of female sexual dysfunction (FSD) and associated risk factors in diabetic women are less clear than in men (Bhasin et al., 2007). Sexual problems in women with DM may be explained by several possible mechanisms, including biological, social, and psychological factors (Rockliffe-Fidler and Kiemle, 2003): 1.Hyperglycemia may reduce the hydration of mucous membranes in the vagina, leading to decreased lubrication and dyspareunia; 2. Increased risk of vaginal infections increases the risk of vaginal discomfort and dyspareunia; 3. Vascular damage and neuropathy may result in decreased genital blood flow, leading to impaired genital arousal response; and 4. Psychosocial factors such as adjustment to the diagnosis of DM, the burden of living with a chronic disease, and depression may impair sexual function (Giraldi and Kristensen, 2010).

7. Relationship between lifestyle, diabetes mellitus and infertility

Life style habits like smoking, diet, and exercise have an impact on health (Anderson et al., 2010). Obesity is associated with a range of adverse health consequences and this leads to an increased risk of diabetes. Obesity and low weight can impact on reproductive function (Fedorcsak et al., 2004). There is strong evidence of the adverse effects of smoking on fertility. In men, smoking negatively affects sperm production, motility, and morphology, and is associated with an increased risk of DNA damage (Kunzle et al., 2003). There is an increasing body of evidence that shows that life style factors can impact on reproductive performance. Multivariate logistic regression reveals that smoking habits and obesity are significant major contributors for infertility in DM men. Bener et al. (2009) suggest that a lifestyle modification program that includes exercise and improved dietary habits need to be established to lose weight, improve fitness and improve reproductive functioning (Bener et al., 2009). In addition to diabetes, other co-morbid factors for infertility include hypertension, erectile dysfunction, varicocele, and sexually transmitted diseases.

According to a recent review, there are few studies of obesity and male factor infertility amongst couples presenting for infertility treatment (Hammoud et al., 2008). However, the results of the studies that were reviewed generally suggest that there is a relationship between male infertility and an elevated BMI (Hammoud et al., 2008).

Both exercise levels and diet impact upon weight and BMI and may therefore affect fertility. Despite the lack of evidence, given the known health benefits of regular exercise and a balanced, nutritious diet, people trying to conceive are advised to exercise moderately and follow a specific type of diet during the preconception period and beyond (Gardiner et al., 2008, Moore and Davies, 2005). In the general population, female and male fertility is decreased by being both overweight (having a body mass index (BMI) of >25 kg/m^2) and underweight (having a BMI of <20 kg/m^2) (Hassan and Killick, 2004, Ramlau-Hansen et al.,

2007). Fertility treatment is also less successful in overweight or obese women (Fedorcsak et al., 2004, Homan et al., 2007, Lintsen et al., 2005, Maheshwari et al., 2007, Tamer Erel and Senturk, 2009). There are a number of dietary factors that impact upon the human reproductive system.

Heavy alcohol consumption has been shown to affect both female and male fertility (Grodstein et al., 1994, Hakim et al., 1998, Klonoff-Cohen et al., 2003, Windham et al., 1992). In men, alcohol consumption can induce testicular atrophy, impotence, reduced libido and cause a deterioration in sperm count (Donnelly et al., 1999, Muthusami and Chinnaswamy, 2005, Olsen et al., 1997). In women, alcohol can alter estrogen and progesterone levels and it has been associated with anovulation, luteal phase dysfunction and impaired implantation and blastocyst development (Gill, 2000). However, it is unclear from the evidence exactly what level of alcohol consumption has an effect on fertility as a result of the absence of a universal estimation of a 'standard drink' and the fact that self-reported, frequently retrospective data on drinking alcohol are a potential source of bias in located studies (Mukherjee et al., 2005).

Although the precise effect of alcohol use on the risk of diabetes has not been clearly established, evidence suggests that moderate alcohol consumption is associated with a decreased risk of diabetes, while heavy alcohol consumption is associated with an increased risk. Furthermore, the ingestion of moderate amounts of alcohol by diabetics has no acute effect on glycemic control (Howard et al., 2004). A plausible biological mechanism by which moderate alcohol consumption may reduce diabetes risk is less apparent. Alcohol consumption was not found to be associated with changes in fasting insulin levels, a marker of insulin resistance, on longitudinal analysis (Moller and Jespersen, 1995). It is possible that moderate alcohol consumption is a marker for a healthy lifestyle that was not entirely accounted for by adjusting for physical activity and diet (Howard et al., 2004). Moderate alcohol consumption is safe and may be beneficial with regard to cardiovascular risk in diabetics. The effect of alcohol use on the risk of other diabetic complications, including retinopathy, remains uncertain (Howard et al., 2004).

Caffeine, a mild neurostimulant, is the most popular pharmacologically active substance consumed worldwide. Caffeine is found in various food products and beverages, including coffee, tea, chocolate, cocoa products, soft and energy drinks and is also present in certain prescription and non-prescription medications, such as cold and influenza remedies, allergy and headache treatments, diet pills, diuretics and stimulants. A majority of the studies on caffeine and reproductive outcomes present conflicting results and should be interpreted with caution due to numerous methodological shortcomings, such as the following: inaccurate estimation of caffeine consumption; recall bias as result of retrospective assessment of caffeine intake, failure to allow for individual variations in caffeine metabolism; and inadequate control for confounding factors. Evidence suggests that consuming caffeine is associated with an increased time to conception, with a possible dose–response effect (Bolumar et al., 1997, Hatch and Bracken, 1993, Stanton and Gray, 1995). However, when adequately considered alongside other lifestyle factors related to fertility,

particularly maternal age, cigarette smoking and alcohol intake, there is little evidence to support the detrimental effect of mild to moderate caffeine consumption on fertility (Leviton and Cowan, 2002, Nawrot et al., 2003).

For reasons of ethical concern and under-reported use of recreational drugs, the evidence about the effect of drug on human reproductive function is sparse and research has been mainly conducted in the form of animal studies (Anderson et al., 2010).

Marijuana is the most commonly used recreational drug worldwide (Battista et al., 2008). Marijuana contains various active components such as cannabinoids that act in both the central and the peripheral nervous system and that interfere with reproductive function at multiple levels. Cannabinoid receptors are located in multiple sites, including reproductive organs such as the ovary, the uterus, the vas deferens and the testis. Acute administration of marijuana in women reduces luteinizing hormone levels, whereas chronic use leads to tolerance and unchanged hormone levels (Park et al., 2004). Cannabinoids can affect fertilisation, oviductal transport and foetal and placental development by dysregulating signalling pathways involved in reproduction and by causing hormonal dysregulation (Battista et al., 2008, Rossato et al., 2008). The existing human data on illicit opiates and reproductive function in women are equivocal and inconclusive (Battista, Pasquariello et al., 2008). Cocaine has been shown to impair ovarian responsiveness to exogenous gonadotrophins in non-human primates and to adversely affect spermatogenesis in rodents (George et al., 1996, Thyer et al., 2001). Abnormal sexual function is common in heroin-addicted men and persists after withdrawal of heroin (Wang et al., 1978). Deterioration of all the sperm parameters, predominantly abnormal motility, have been demonstrated in the majority of heroin-addicted males and to a lesser extent in methadone users (Ragni et al., 1988, Ragni et al., 1985). Normal levels of serum gonadotrophins, with a significant elevation in prolactin and decrease in total and free testosterone levels, were reported in opiate-addicted men (Ragni et al., 1988, Ragni et al., 1985). The effects of cocaine and heroin use during pregnancy include placental disruption, pre-term delivery, low birth weight, neonatal mortality, neonatal withdrawal syndrome and possible long-term neurobehavioral effects, some of which can be associated with poor prenatal care and other substance use rather than purely attributed to cocaine (Hulse et al., 1998, Richardson et al., 1993).

Couple experiencing infertility generally report that is a stressful experience (Anderson et al., 2010). The stress may arise from unfulfilled self-expectations, social pressure, undergoing evaluation and treatment, disappointment with failures and the financial costs associated with the whole process. Infertile women have a significantly higher prevalence of psychiatric disorders relative to fertile women (Chen et al., 2004). Infertile men appear to experience significant distress with transient episodes of impotence and sexual performance anxiety which may contribute to difficulties in achieving natural pregnancy (Peterson et al., 2007, Shindel et al., 2008). Psychological stress has been considered the most common reason for discontinuation of fertility treatment before achieving pregnancy (Olivius et al., 2004, Rajkhowa et al., 2006) and pre-treatment levels of depression have been shown to be highly predictive of patient dropout behavior after only one IVF cycle (Smeenk et al., 2004). Besides

stress-related sexual dysfunction and discontinuation of treatment, stress exposure has been directly related to reproductive failure. The pathophysiological rationale behind this assumption is a complex immune-endocrine response to stress that disturbs equilibrium and there is evidence of a stress-associated suppression of reproductive function including the delaying of menarche, hypothalamic amenorrhea, ovarian dysfunction and early-onset perimenopause (Nakamura et al., 2008, Nepomnaschy et al., 2007).

Despite spermatogenesis being a function of only the mature testis, environmental injury during maternal, perinatal and prepubertal phases can indirectly influence eventual sperm production in the adult male. It is believed that exposure during these phases of the developing testis leads to irreversible effects on spermatogenesis, while the accompanying effects of adulthood exposure are in all probability reversible (Dinulovic and Radonjic, 1990).

Evolution has caused our bodies to adapt to their environment. This connection is vital for reproduction as the birth of the young must coincide with plentiful food, and thus increase the chances of survival (Sharpe and Franks, 2002). Although human reproduction is not season specific, sexual behavior and reproduction is notable all year round. Fertility is influenced profoundly by our environment including season and food intake (Sharpe and Franks, 2002).

8. Treatments and solutions for the infertile DM patient: lifestyle changes

Infertility is a global problem. It affects all socioeconomic levels, racial, ethnic and religious groups. Fortunately, in the majority of cases, there is a specific cause for infertility that can be medically resolved. In fact, only about 10% of infertility cases go unexplained.

When a couple seeks medical help, one of the first conditions the doctor will look for is diabetes since the condition can cause fertility complication in both genders. In most instances, simple lifestyle changes like adequate nutrition and weight loss through proper exercise can help reverse the effects of infertility (Figure 2). Fortunately, most cases of infertility, which are related to diabetes, can be treated. In cases where infertility is related to insulin levels, correcting the imbalance is often enough to result in a successful pregnancy. Normal levels of blood sugar are needed to succeed in becoming pregnant. This means insulin, HgbA1c and hemoglobin levels as well as weight need to be monitored. For Type 1 diabetes, insulin replacement therapy is the main treatment regime to be followed as prescribed by the treating physician. Furthermore, when a diabetic subject, exercises properly and ensuring adequate nutrition with a vitamin supplement the chances of conception are improved. Regular exercise helps weight loss and also aids the body in reducing blood glucose levels and in using insulin more efficiently. Newer approaches to treating infertility caused by diabetes and its complications include morbidly obese women undergoing bariatric or gastric bypass surgery (for weight loss). Preliminary successful results have been reported as diabetic women are now able to conceive as they lose weight.

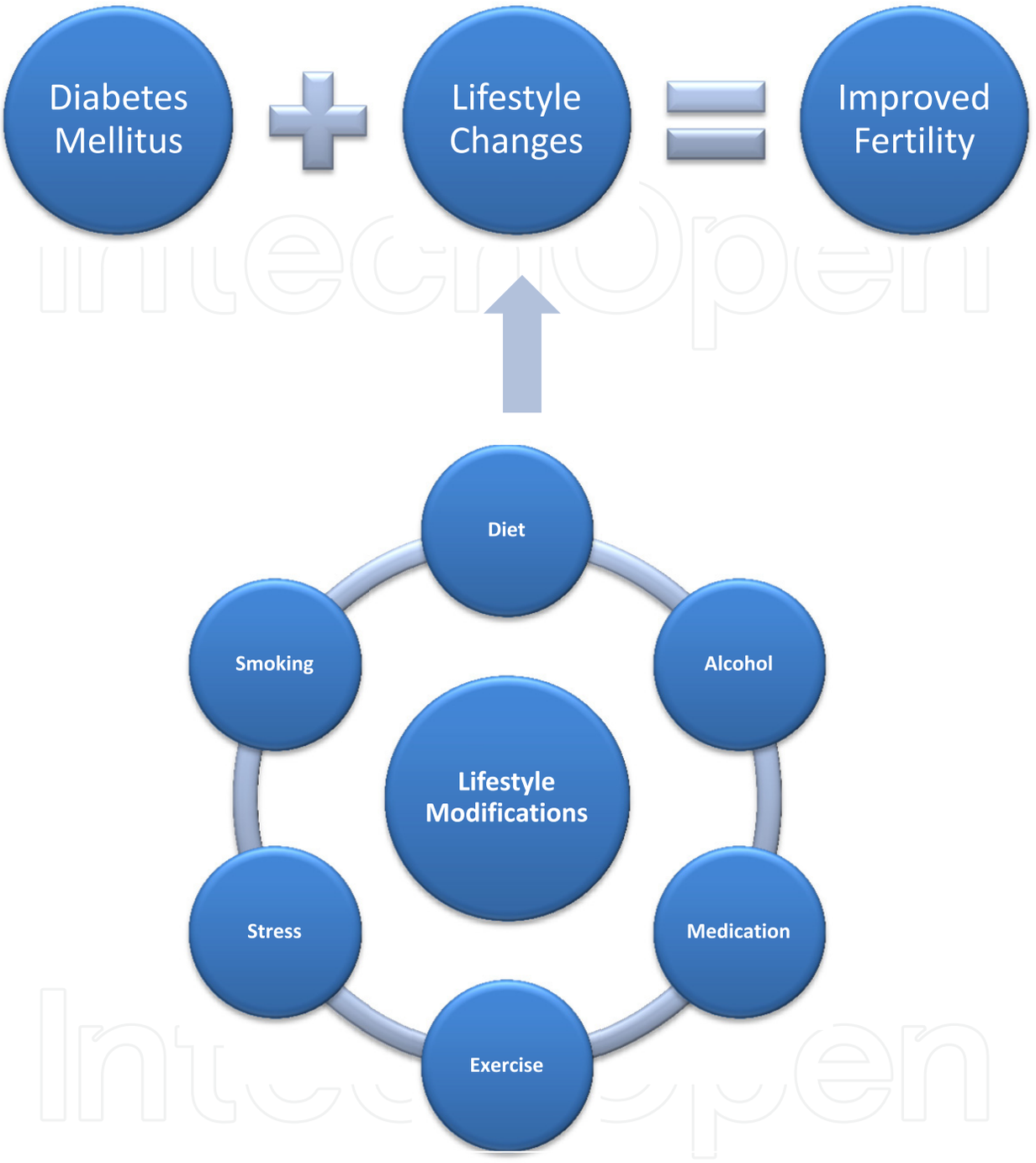

Figure 2. Lifestyle modifications in the DM patient that can help improve fertility

Insulin resistance can be managed with modified diet, exercise, and drugs such as metformin. Exercise programs, vitamin supplements and weight loss alone will better ovulation in one-third of patients. When Clomiphene Citrate, Metformin and Letrozole are used to treat the remainder of infertility patients, more than 80% of infertile couples are able to conceive, as long as there are no other infertility problems reported. This benevolent effect is due to these lifestyle changes and adequate medical intervention in due time (Du

Plessis et al., 2010). Once conception is achieved, the challenge is to control blood sugar levels so that the pregnancy can be carried to full term. The best way to prevent miscarriage in women with PCOS is to normalize hormone levels to improve ovulation, and normalize blood glucose and androgen levels. In recent time, more doctors have been prescribing the drug metformin to help with this problem.

Women who have a body mass index above 35 should lose weight before conception, and this should be an integral part of any fertility program's management of all overweight and obese patients. Weight loss of 5-10 per cent of total body weight can achieve a 30 per cent reduction of visceral adiposity, an improvement in insulin sensitivity, and may help with restoration of ovulation. More often than not, pharmacotherapy for fertility is needed in addition to all these lifestyle changes and thus, the expert management of a fertility specialist is pivotal.

Women with Type 2 diabetes, there have shown a higher incidence of secondary hypogonadotropic amenorrhea (low sex hormones leading to absence of periods), exacerbated by body mass index that is low and glycosylated hemoglobin (HbA1c) that is higher than normal. In women with diabetes mellitus desiring pregnancy, pre-pregnancy counseling is essential before conception is critical to diminish the risk of spontaneous abortion, fetal abnormalities, macrosomia (abnormally big baby), and other pregnancy complications. Diabetic women should aim for a HbA1clevel of below 6 %, or below 7 % if the risk of hypoglycemic episodes is too high, before pregnancy.

Other lifestyle changes or tips for helping fertility in diabetics include: avoiding cigarettes and any drugs that may affect sperm count or may reduce sexual function; getting sufficient rest and reducing stress; males must prevent overheating of the testes and should avoid hot baths, showers, and steam rooms, while avoiding tight underwear; and avoiding use of sexual lubricants, as they may affect sperm motility (Du Plessis et al., 2010).

If fertility issues remain unresolved, intrauterine insemination (also called artificial insemination) and assisted reproductive technologies, such as in vitro fertilization, may be considered.

With careful management of this disorder, people can live long healthy lives and the effects on fertility can be reduced notably.

9. Conclusion

Diabetes mellitus can be either directly or indirectly associated with several disorders of the reproductive system and sexual function. Several studies have demonstrated that diabetes could be prevented by weight loss, regular exercise, modification of diet, abstinence from smoking, and limiting the consumption of alcohol. Weight control would appear to offer the greatest benefit. Education of diabetes is an important first step in order to make healthy lifestyle choices and manage the condition effectively.

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