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Mini Review

Type-1 Diabetes Mellitus and its Relation with Impairment of Female Fertility

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Abstract

Type 1 and type 2 Diabetes mellitus have shown a profound effect on the reproductive potential of women. Many women with reproductive abnormalities have been diagnosed with diabetes as a major cause of reproductive failure. Diabetes reduces the reproductive period of women due to delayed menarche and early menopause. The diabetic women show menstrual irregularities, anovulation, oligomenorrhea, secondary amenorrhea. The possible preventive measure could be glycemic control for the management of T1DM related reproductive dysfunction. This mini-review will focus on the type 1 Diabetes and its relation with female reproductive impairments at different stages of female reproductive phase. The management strategies for diabetes-related reproductive impairments are still elusive and needs further study.

Keywords: Diabetes Mellitus; Female; Fertility

Introduction

Infertility is defined as failure to get pregnant after trying for 1 year or 6 months for women over 35 years of age. According to the World Health Organization (WHO), 8-10% of the couple are infertile and it is directly related to the social, financial and personal problem [1]. The incidence of infertility has increased in recent years and it is implicated to lifestyle modifications, drug abuse, smoking, environmental and social-economic factors. The problem in fallopian tube, uterus, ovaries and menstrual disorders are the main cause of female infertility. Moreover, diabetes has been associated with metabolic abnormalities causing menstrual disorders leading to infertility [2]. Recent investigations have claimed women with type 1 diabetes (T1DM) have fewer offspring and increased congenital abnormalities than healthy women [3,4]. However, the fertility of Asian women with T1DM still needs further investigation.

The type 2 diabetes mellitus (T2DM) is considered as a silent killer and is a complex heterogeneous disease spreading at an alarming rate worldwide even in developing countries (Xu., *et al*. 2012; Foo., *et al*. 2010). In India, the expected number of patients with T2DM may cross 87 million by the end of 2030 (Ramchandran., *et al*. 2010). The manifestation of T2DM includes chronic hyperglycemia, insulin resistance, decreased insulin secretion. Hyperglycemic state in T2DM condition even leads to morbidity and mortality (Su., *et al*. 2010). Other dysfunctions include retinopathy, neuropathy, nephropathy, cardiopathy, lipotoxicity, etc. (Baccetti., *et al*. 2002; Barros., *et al*. 2006; Minokoshi., *et al*. 2002). In addition, T2DM patients also show increased oxidative stress, β-cell impairments, inflammation (Baynes., *et al*. 1999; Yu., *et al*. 2017). Recent evidence has also stated that women with T2DM showed a greater risk of developing polycystic ovaries compared to healthy women [5,6]. The women with higher body mass index (BMI) showed poor quality of blastocyst formation [7].

Type 1 Diabetes mellitus and menstrual disturbances

Only 2% of women with T1DM showed successful pregnancy after a defect in menses [8]. The insulin treatment to this T1DM can cure the menstruation but did not eliminate menstrual irregularities. The T1DM females showed three times more frequency in amenorrhea and oligomenorrhea [9]. The T1DM women with menstrual irregularities have also shown to develop

early aging and osteoporosis and cardiovascular disease. It has also been reported that menstrual disturbance was twice frequent in T1DM females compared to healthy females [10]. In a previous study, 24 adolescent females having uncontrolled metabolism and higher BMI, about 54% of them showed menstrual irregularities [11]. The T1DM girls showed higher menstrual irregularities having HbA1c more than 10% [12]. Thus it is clear that anovulatory condition in T1DM is the result of menstrual disturbances. In a study, the healthy and T1DM girls showed a similar frequency of anovulatory cycle after menarche. However, following the second year, the frequency of the ovulatory cycle was more in healthy girls than T1DM girls [12]. The reason for the menstrual disorder in T1DM females may include decreased LH secretion, delay in positive estrogen loop and development of hyperandrogenism [13-15].

T1DM and hypothalamic control of the menstrual cycle

The secretion of gonadotropin-releasing hormone (GnRH) in a pulsatile manner is a driving force for the active role of H-P-G axis by releasing pituitary gonadotropin Luteinizing hormone (LH) and follicle stimulating hormone (FSH). Earlier findings suggest a decrease in LH secretion in T1DM female with amenorrhea [16]. In diabetic animal insulin therapy did not affect the gonadotropin release, thus the main factor for hypothalamic impairment in T1DM female is the inadequate release of GnRH [17]. The alloxan induced T1DM pre-pubertal rat did not show ovulation and failed to show the LH peak [18]. In addition, a group of women presented a lower estrogen level in T1DM condition from follicular to luteal phase [19]. This dysfunction may be attributed to hyperinsulinaemic condition leading to a defect in glucose metabolism and binding of hormones to its target receptor in the central and peripheral system. The T1DM females also showed permeability to dopamine in the hypothalamus which normally does not cross the brain barrier [20]. The penetrance of dopamine inhibits the LH and FSH secretion which in turn causes metabolic abnormalities [21].

T1DM and Ovarian function

Although T1DM female show hypogonadism with disturbed metabolism in some cases, hypergonadism is also seen as a result of increased insulin level to the ovary. Insulin receptors are localized in thecal cells, granulosa cells and stromal cells of the ovary [22]. The insulin signaling in the ovary increases steroid production from thecal cells by upregulating steroidogenic enzymes which causes hyperandrogenemia in T1DM females [22]. The T1DM also show increased folliculogenesis and ovarian volume mediated via increased insulin signaling on granulosa cells [23].

In addition, recent findings suggest that hyperglycemia induced by streptozotocin injection in rat causes ovarian dysfunction. These animals showed diminished follicular growth with smaller pre-ovulatory follicle, delayed oocytes maturation, increased apoptosis of follicles and poor communication between somatic cells and germ cells [24]. Folliculogenesis inT1DM females have been implicated to anti-Mullerian hormone (AMH) level which is the hallmark of ovarian reserve. The pre-pubertal T1DM girls showed elevated AMH level which indicates insulin role in promoting the growth of the small follicle [25]. Thus several factors are involved in modulating ovarian function in T1DM female. The decline in insulin production may lower the gonadotropin secretion due to decreased GnRH secretion.

T1DM and puberty

It has already been discovered that girl with T1DM tend to show a delay in puberty [12]. In the early 1980s and 1990s, insulin therapy was given as a remedial protocol for the pubertal delay. The result showed improvement in pubertal delay but 6 months to a 1-year delay in breast development [26,27]. In addition, the latch in T1DM girls appeared 6 months later compared to the control subject [28]. There has been a significant delay in menarche defined for the women with T1DM during the 20th century. During 1940-50 menarche occurred 2 years after in T1DM female compared to healthy female [29]. During 1970-80 girls with T1DM the delay in pubertal maturation was advanced to 1 year compared to control [30]. The clinical manifestation of menarche is related to its magnitude and associated with late menses and other endocrine abnormalities [31]. The hormonal mechanism involved in pubertal delay has been attributed to delay in gonadotropin release and lower insulin doses associated with T1DM [32]. Other possibilities associated with pubertal delay is the presence of ovarian antibodies, insulin resistance and higher SHBG leading to reduced availability of steroids [14,33,34].

T1DM and adult female

Adult females of reproductive age have more reproductive complications than boys. The T1DM adult females had excessive weight gain and irregular menses, particularly oligomenorrhea [35]. Almost 60% of T1DM females suffer from oligomenorrhea compared to healthy females [36]. Despite menstrual irregularities, T1DM female and healthy female had a similar ovulatory rate [25]. Secondary amenorrhea has also become frequent in T1DM females compared to healthy females [36]. The menstrual irregularities associated with T1DM have been implicated to metabolic abnormalities. It has been observed that HbA1c plays an important role in determining the length of the menstrual cycle and with 1% increase in HbA1c the cycle was prolonged for 5.1 days [36].

PCOS and T1DM

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in the female of reproductive age. It is characterized by hyperinsulinemia, anovulation, and hyperandrogenism [37]. The T1DM females generally showed hirsutism in almost 20-30% of young adult females [38]. The T1DM and PCOS females showed a lesser extent of hyperandrogenism compared to PCOS non-diabetic females. The hormonal profile is also different in T1DM females with PCOS compared to non-diabetic PCOS females [39]. Free androgens are also decreased in T1DM having PCOS. The LH and FSH levels are also reduced in T1DM and PCOS females. Thus the increased androgen level is mainly of ovarian origin [39,40].

The possible preventive mechanism for T1DM is still under study. The addition of non-androgenic oral contraceptives, metformin, and other insulin sensitizers may help in reducing symptoms. The T1DM treated with metformin in combination with flutamide showed a beneficial effect on hyperandrogenism.

Conclusion

T1DM is a state of metabolic disturbance affecting the normal reproductive function of women throughout life. The T1DM generally affects every stage of female reproductive life, from pre-puberty to reproductive adult stage. The T1DM suffers from amenorrhea, oligomenorrhea, etc. The preventive measure for the effective treatment of T1DM related infertility is less understood and needs further clarification. The future clinical management of T1DM may include the establishment of anti-ovarian autoantibodies, their association with glycemic control and preventing fertility.

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Conflict of Interest

Declared none.

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