FERTILITY ISSUES IN WOMEN WITH DIABETES MELLITUS

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ABSTRACT
Diabetes mellitus Type 1 and Type 2 should be considered in the differential diagnosis of menstrual abnormalities and infertility. The reproductive period of diabetic women may be reduced due to delayed menarche and premature menopause. During the reproductive years, diabetes has been associated with menstrual abnormalities, such as oligomenorrhea and secondary amenorrhea. It was found that better glycemic control and prevention of diabetic complications improves these irregularities and increases fertility rates close to those that are seen in the general population. Women with persistent menstrual abnormalities despite adequate treatment need to be approached by broader evaluation, which will include the examination of the hypothalamic–pituitary–ovarian axis and the hormonal status, presence of autoimmune thyroid disease and antiovarian autoantibodies, and hyperandrogenism.

KEYWORDS: diabetes Mellitus, menstrual abnormalities, infertility.

INTRODUCTION
Diabetes is a disease that affects millions of people and their families. The WHO estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030.

Type 1 diabetes, which predominately affects youth, is rising alarmingly worldwide, at a rate of 3% per year. Some 70,000 children aged 14 and under develop Type 1 diabetes annually.
Type 2 diabetes is also increasing in number among children and adolescents as obesity rates in this population continue to soar, in both developed and developing nations.

Diabetes affects women in many ways, and one of them will be the focus of the present review – the association between diabetes mellitus and infertility.

Menarche & Menstrual Cycle Disturbances in Type 1 Diabetes.

Before the first introduction of insulin in clinical care of Type 1 diabetes in 1922, menarche rarely occurred in girls with diabetes during childhood, and when it did occur, menses usually ceased. Successful pregnancy was achieved in only 2% of Type 1 diabetic women.

Initiation of insulin treatment caused menstruation to appear in most female diabetic patients, but did not abolish menstrual irregularities. Earlier studies from 1954 by Bergqvist showed delayed menarche among women with the onset of diabetes before menarche and controlled for their diabetes mellitus as outpatients, together with persistent menstrual disorders remaining in the third and forth decade in 30% of those women. The prevalence of these disorders, mainly secondary amenorrhea and oligomenorrhea, was shown to be three-times more frequent compared to nondiabetic controls in the study by Rzepka et al. in 1977.

Subsequent epidemiologic studies supported the fact that diagnosis of Type 1 diabetes prior to menarche, particularly before 10 years of age, caused a delay in menarchial age of approximately 1 year when compared with control. Similar results were obtained in studies conducted in different demographic populations. Moreover, a correlation was found between the menarchial age delay and the presence of menstrual irregularities. Kjaer et al. found menstrual dysfunction to be twice as frequent in diabetic women compared with nondiabetic controls (21.6 vs 10.8%), which is lower than reported by Bergqvist, but no less bothersome. In addition, in Strotmeyer's study, Type 1 diabetes was independently associated with longer cycle length (>31 days), long menstruation (≥6 days), heavy menstruation, and more reports of any menstrual problem at the younger age ranges (<29 years). As women moved closer to the end of their reproductive years, the differences found by diabetes status were no longer significant.
The effect of Type 1 diabetes on the reproductive endocrine axis can be conceptualized as anorexia-like hypothalamic anovulation. Diabetic women with low BMI are more likely to have menstrual irregularities.

There are catabolic processes in young diabetic girls and nutritional restriction leads to intracellular starvation, especially before the diagnosis and initiating insulin treatment. This may subsequently cause disruption in hypothalamic pulsetile secretion of gonadotrophin-releasing hormone (GnRH), with a resultant decrease in gonadotropins secretion.

In diabetic animal studies conducted by Johnson and Sidman in 1979, it appeared that the main etiologic factors associated with impaired hypothalamus–pituitary function were indeed inadequate release of GnRH and/or reduction in the sensitivity of the pituitary gland to GnRH. Studies in women by Djursing et al. in 1983 and 1985 detected lower basal levels of luteinizing hormone (LH) in Type 1 diabetic patients with amenorrhea, and showed different reactions of LH to exogenous GnRH, thus suggesting that menstrual disturbances in Type 1 diabetic patients are mainly of hypothalamic origin rather than primary pituitary dysfunction.

Neuroendocrine control must also be considered when interpreting disturbances in the HPO axis. It was reported by Djursing that Type 1 diabetic women had lower basal prolactin levels, unrelated to the presence of menstrual disorders. However, only diabetic amenorrheic patients had a decreased prolactin response to dopamine antagonists. These results suggest that diabetic patients with menstrual disorders may have increased central dopaminergic activity, which in turn inhibits GnRH secretion. Endogenous opium-like peptides – endorphins – also have an inhibitory effect on GnRH release. It is believed that gonadotrophin secretion is regulated by an interaction between dopamine and endogenous opioids. Nevertheless, a previous study by O'Hare et al. in 1987 failed to demonstrate a change in gonadotrophic levels or initiation of menstruation after administration of the opioid inhibitor naloxon in hypogonadotrophic amenorrheic Type 1 diabetic women. Finally, an association between Type 1 diabetes and polycystic ovary syndrome (PCOS) was reported in a recent study by Codner et al. These authors found that vigorous treatment with insulin, frequently applied in Type 1 diabetes in order to prevent diabetic complications, may lead to supraphysiological doses of insulin, subsequently initiating hyperandrogenism and PCOS. In addition to exogenous hyperinsulinism, insulin resistance is also possible in women with Type 1 diabetes, owing to decreased glucose uptake by the muscle. That also contributes to the development of androgen excess in women with Type 1 diabetes. Codner et al. detected
increased levels of total and free testosterone, increased LH to follicle-stimulating hormone ratio, larger ovarian volumes and abnormalities in ovarian morphology. This was especially prominent among women with the onset of Type 1 diabetes before menarche. PCOS prevalence of 31 and 40% were reported using the Androgen excess society criteria and Rotterdam criteria, respectively, among Type 1 diabetic women in Codner's study.

**Correlation between Type 2 Diabetes & Fertility**

Most of the Type 2 diabetes female patients are postmenopausal women, but with changing dietary and lifestyle patterns, the prevalence of obesity is increasing, thus raising the incidence of Type 2 diabetes during the reproductive years.

There is an association between Type 2 diabetes and fertility, alterations in the length of the menstrual cycle, and the age of onset of menopause. This association may be explained by linking this disease to PCOS, the most common hormonal disorder among women of reproductive age, and a leading cause of infertility. Insulin resistance, obesity and diabetes mellitus strongly correlate with PCOS. Both PCOS and Type 2 diabetes have the same risk factors, such as hypertension, obesity, dyslipidemia and hyperinsulinemia. Hyperinsulinemia results from insulin resistance, which through alterations in the level of IGFBP, IGF1 and SHBG stimulates increased androgen secretion at the adrenal gland and the ovary, subsequently causing anovulation. Legro et al. showed that PCOS women are at significantly increased risk for impaired glucose tolerance and Type 2 diabetes mellitus at all weights and at a young age. They also found that these prevalence rates are similar in two populations of PCOS women with different weights, suggesting that PCOS may be a more important risk factor than ethnicity or race for glucose intolerance in young women. By contrast, a study by Amini et al. showed that PCOS is highly prevalent in Type 2 diabetic patients. Obesity is common in both PCOS and Type 2 diabetic women. Studies show that obese women seeking pregnancy experience longer times to conception, unrelated to age and to cyclic regularity, which is suggestive of alterations in ovarian function during the periconceptional period. Metwally et al. found that oocytes from women with increased BMI gave rise to blastocyts of poorer quality. A recent study presented an analysis of the ovarian follicular environment of women across a large range of BMIs, by measuring follicular fluid hormones and metabolites, as well as granulosa and cumulus cell gene expression. The study demonstrated elevated intrafollicular insulin and triglycerides, and increased expression of lipoprotein receptors in overweight and obese women. Gene expression alterations were not affected by
BMI. In addition, there was an increase in free androgen profile within the ovarian follicles of obese women, as well as an increased level of C-reactive protein, which may be associated with the poorer reproductive outcomes typically observed in these patients.

Finally, systematic review on pregnancy and fertility following bariatric surgery showed that some normalization of sex hormones and menstrual irregularities, as well as improvement in PCOS, has occurred. However, the influence on fertility still needs to be further studied.

Association of Modern Management of Diabetes Mellitus Type 1 with Decrease in Infertility.

In the past, the relationship between menstrual dysfunction and diabetic control was considered controversial. Kajer et al. showed an association between low BMI, high concentrations of HbA1C and the presence of menstrual irregularities. Yeshaya et al. found that patients with diabetic complications had a higher incidence of menstrual disorders compared with diabetic patients without complications. Schroeder et al. examined the correlation between the degree of glycemic control in Type 1 diabetic adolescents and menstrual regulation. They reported that tighter glycemic control, measured by lower levels of HbA1C, was associated with improved menstrual regulation. Other studies failed to demonstrate a relationship with the metabolic state (high BMI, microvascular and macrovascular complications, or high HbA1C. There have even been reports suggesting good metabolic control among women with oligo/amenorrhea.

The first population-based epidemiological study on fertility rates over time among women with Type 1 diabetes was conducted in Sweden during 1965 to 2004. The study followed up on 5978 Type 1 diabetic women diagnosed at 16 years of age or younger, who were identified in the Swedish Inpatient Register, until 48 years of age, death or emigration. A standardized fertility ratio (SFR; the ratio of observed to expected number of live births, with 95% CIs), was used to express the relative fertility rate. The number of live births was 4013, which was smaller than expected (SFR 0.80 [95% CI: 0.77–0.82]). The lowest SFRs were observed among women who had their first hospitalization for diabetes in the earliest years. Overall, fertility among Type 1 diabetic women was reduced by 20% in this study, compared to the matched general Swedish female population, with the lowest SFRs in the earlier years. This was followed by a significant increase in SFR until normalization among women with uncomplicated disease and an onset in the past 20 years. The increase in fertility after 1985
was independent of complication status, age at first hospitalization or duration of diabetes, and thus was probably attributed to better interventions in treatment. Although improvement was evident regardless of status of diabetes complications, women with complications always had lower fertility than those without these complications.

The results of this study suggest that the stricter metabolic control exercised in the past 20 years, together with better control of blood pressure and more frequent use of drugs active in blocking the renin–angiotensin system, has also been successful with regard to preserving fertility.

**Autoimmunity**

Autoimmune diseases, including oophoritis, orchitis and hypothyroidism, are well-known causes of infertility. Autoimmune oophoritis may occur as part of type I and type II syndromes of polyglandular autoimmune failure, which are associated with autoantibodies to multiple endocrine and other organs. Young women with spontaneous premature ovarian failure are at increased risk of autoimmune hypothyroidism and should be screened for this condition.

Type 1 diabetes and autoimmune thyroid diseases frequently occur together within families and in the same individual. Therefore, we can assume that patients with Type 1 diabetes that have overt or concealed hypothyroidism may also be at risk for premature ovarian failure. In general, evaluation of premature ovarian failure should include serum concentration of follicle-stimulating hormone and estradiol and screening for asymptomatic autoimmune adrenal insufficiency, since it is more common in women with autoimmune ovarian failure. In addition, testing should include thyroid-stimulating hormone, free T4, antithyroid-peroxidase, antithyroglobulin antibodies and karyotype.

Menstrual cycle changes observed in patients with Hashimoto's thyroiditis include menorrhagia, more frequent and longer periods, and dysmenorrhea. Prevalence of thyroid autoimmunity is significantly higher among infertile women than among fertile women, especially among those whose infertility is caused by endometriosis or ovarian dysfunction.

The role of thyroid involvement in diabetes Type 1 patients and its effect on menstruation cycle and fertility has been well observed. More studies, however, are needed to explore the
correlation between Type 1 diabetic women and the presence of antiovarian autoantibodies among these women, with relationship to infertility.

**Sexual Dysfunction & Diabetes**

It is been estimated that approximately 35–75% of men with diabetes will experience at least some degree of erectile dysfunction during their lifetime. They tend to develop erectile dysfunction 10–15 years earlier than men without diabetes. The effect of diabetes on female sexual function was not fully recognized and addressed in the past. Enzlin et al. reviewed 15 studies conducted between 1971 and 1996, and documented that the prevalence of impaired sexual arousal and inadequate lubrication was between 14–45% among diabetic women, significantly higher than in healthy controls. In a subsequent controlled study that they conducted in 2002, Enzlin et al. found that more women with diabetes than control subjects reported sexual dysfunction (27 vs 15%; p = 0.04). Female sexual dysfunction may have a secondary effect on fertility by decreasing sexual desire and limiting sexual activity, especially around the time of ovulation.

**Future Perspective**

Improved glycemic control was found to be associated with improvement in menstrual abnormalities and in fertility rates. Nevertheless, some diabetic patients experience persistent menstrual irregularities even though good metabolic control has been achieved. In those patients, it is worthwhile to address the possible abnormalities in the HPO axis and to evaluate their hormonal status (GnRH, LH, follicle-stimulating hormone and GnRH stimulation test), as well as the autoimmune etiology related to diabetes.

At present, most of our knowledge on autoimmunity aspects of Type 1 diabetes and its effect on fertility in diabetic women is mainly related to the presence of Hashimoto's thyroiditis or thyroid peroxidase autoantibodies. Few studies have explored the presence of antiovarian autoantibodies and its clinical significance in Type 1 diabetes patients. Snajderova showed a higher prevalence of these antibodies in Type 1 diabetic girls, but there has not been further follow-up. More studies need to be conducted in order to examine the correlation between Type 1 diabetic patients and the presence of antiovarian autoantibodies. Additional questions remain whether antiovarian autoantibodies are associated with infertility, and whether tight glycemic control may decrease or eliminate their prevalence.
Premature menopause observed more commonly among diabetic women is also a mystery that remains to be solved. Several explanations have been proposed, among them the antiovarian autoantibodies, prolonged hyperglycemia and hyperandrogenism induced by insulin treatment. Future studies should be conducted to evaluate the relationship between better metabolic control and the age of menopause in diabetic patients.

Finally, we mentioned the possible effect that diabetes may have on the incidence and the severity of upper genital tract infections. Few studies have been reported until now exploring this field, and this possible association and its effect on fertility definitely deserve further research.

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