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ORIGINAL ARTICLE

Reproductive disturbances in type 1 diabetic women

Wiesław Zarzycki & Magdalena Zieniewicz

Department of Endocrinology, Diabetology, and Internal Medicine, Medical University of Bialystok

Correspondence to: Dr. Wieslaw Zarzycki
Departament of Endocrinology, Diabetology, and Internal Medicine,
Medical University of Bialystok
15-273 Bialystok, M. Skłodowskiej-Curie 24A , POLAND
TEL. +48(0)85-7468607; FAX +48(0)85-7447611
EMAIL: wieslawzarz@wp.pl

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Abstract

Among young type 1 diabetic women disturbances of reproductive system and other related disorders are often present. The present paper, which reviews the literature of the past several years aims to present some of those disorders. Special attention is focused on menstrual irregularities, fertility and sexual problems. Type 1 diabetic women usually have a delayed menarche and an early onset of menopause than nondiabetic women. They are also at higher risk of having menstrual disturbances, such as amenorrhea and oligomenorrhea. It has been suggested that the GnRH pulse-generator in the hypothalamus is responsible for diabetic menstrual dysfunction. The risk of sexual and gestational problems is higher in type 1 diabetes than in the general population, but fertility in diabetic women seems to be similar to nondiabetics.

Abbreviations & units:

HbA1c	– glycosylated haemoglobin
LH	– luteinizing hormone
FSH	– follicle-stimulating hormone
GnRH	– gonadotropic releasing hormone
SHBG	– sex hormone binding globulin
UTI	– urinary tract infection

Type 1 diabetes mellitus affects mostly young people and it is usually a serious problem for this type of patients. Type 1 diabetic women have the same aims and social needs as their healthy peers. They want to bear children and have a successful career. However, presence of diabetes always affects the physical and psychological aspects of their life. It may worsen the quality of life through the impairment of some physiological processes. Reproductive period disturbances together with other dysfunctions, which may have an effect on the reproductive system, are most important for diabetic women.

Diabetic women, especially those diagnosed before puberty, often have peripubertal disturbances [1, 2, 3, 4]. Later on in life an impairment of vital life processes can be observed in those women: menstruation and fertility disturbances, sexual dysfunctions and urinary tract dysfunctions. The risk of some pathologies in pregnancy and earlier menopause is also increased.

Before an introduction of insulin for the treatment of type 1 diabetes, an enhancement of katabolic processes could be seen in young diabetic girls, which resulted in the impairment of their development. Menarche rarely occurred or menstruation usually cased [5], thus fertility was impaired. Skipper [6] noted that occurrence of pregnancy was highly unusual. Only about 2% of type 1 diabetic women were able to have a successful pregnancy. The reason for obstetrical failure was mostly a high level of mortality among diabetic women [7]. The introduction of insulin therapy greatly improved fertility. The report of Bergqvist

from the years 1938 to 1954 shows that the pregnancy rate was estimated to be 38% lower in women with diabetes than in non-diabetics [1]. However, despite the return of menses and fertility, insulin-treated diabetic women still have an increased incidence of menstrual irregularities in comparison to non-diabetics [1]. In addition etiology and pathological mechanisms are still not defined.

Some investigators observed a delay in menarchial age of about 1 year in type 1 diabetic girls if the onset of diabetes mellitus occurred before puberty [1, 2, 3, 4]. Kjaer [3], similarly to the earlier observations by Bergqvist [1] and Burkart [2], found, that if diabetes develops in childhood, delay in menarche is often seen. But menarchial age is comparable to that seen in non-diabetics if the onset of diabetes mellitus occurred after puberty. That would suggest that menarche is not influenced by genetic predisposition to diabetes but seems to be affected by the presence of clinical diabetes and diabetic metabolic disturbances [3].

Diabetes onset may cause weight loss, decrease in body fat, and the resulting impairment of the transformation of androgens to estrogens. Estrogens are important for the occurrence of menarche. Additionally, hypotetic functional distruption of the hypothalamic-pituitary-gonadal axis by this disease may cause a delay in the menarchial age [8, 9, 10].

Type 1 diabetic women have an increased incidence of menstrual irregularity [1, 3, 6, 10]. Bergqvist [1] reported menstrual abnormalities in 30% of these women. Kjaer, in epidemiological study of menarche and menstrual disturbances found menstrual dysfunction in 21,6% of diabetic women compared to 10,8% non-diabetic controls, in 245 insulin treated diabetic women and 253 healthy women. So menstrual dysfunction was about twice as frequent in diabetic women compared to non-diabetic controls. Oligomenorrhea and secondary amenorrhea are more typical for menstrual dysfunction found in diabetic women. Kjaer reported that 8,2% of the diabetic women and 2,8% of the controls had experienced episodes of secondary amenorrhea; corresponding figures for oligomenorrhea were 10,6% and 4,8%. There seems to be a link between late menarche and these dysfunctions [3]. Strotmeyer [11] showed that type 1 diabetic women have an increased risk of any menstrual problems only at a younger age [<20 and 20–29 years]. While, in non-diabetics these irregularities seem to accumulate in the years closer to menopause, when physiological changes start to occur in gonads. Additionally, insulin-treated diabetic women have longer and heaver menstruation in age ranges <20 and 20–29 years compared to controls [3, 4]

A relationship between menstrual disturbances and diabetic control remains controversial. Kjaer [3] found an association between low body mass index, high concentrations of HbA1c and a presence of oligo/amenorrhea in diabetic women. These findings may indicate that low body mass and poor metabolic control may be partly responsible for the incidence of amenorrhea in this population. Ia Marca [12] has demonstrated that women with amenorrhea had good metabolic control of diabetes suggesting that the amenorrhea is a form of functional hypothalamic insufficiency which can be treated as a theoretically reversible form of ovulatory impairment, requiring psychological and pharmacological management. Djursing et al., while describing a small [n=22] group of diabetic patients with oligo/amenorrhea, has not found any relationship between metabolic state and menstrual irregularity [8]. Strotmeyer [11] and O'Hare [13] also proposed that these disturbances may not be amenable to metabolic control. O'Hare in one of this paper arques, that improvement in metabolic and nutritional status was not associated with a spontaneous return of menstruation and the change in sex hormones profile. Thus the question arises whether hypogonadotropic amenorrhea is an irreversible complication of type 1 diabetes mellitus.

For the better understanding of reproductive period disturbances in type 1 diabetic women, we should consider a relationships between that disease and hormones of menstrual cycle.

Proper menstrual cycle influence on glucose metabolism in diabetes is not defined well enough, similarly to that of diabetes influence on sex hormones [14, 15]. Most type 1 diabetic women had a hyperglycaemia in a fasting state in the luteal phase. Afternoon hypoglycaemia can be caused by: an increase in their insulin dose in response to changes in fasting blood glucose levels or a change in the sensitivity to insulin [16]. Jovanovic-Petersen's 6-months observations reported a significant increase in the insulin dosage in each luteal phase and a quick rise of glucose utilization in this phase at about 10.00 a.m. These results have showed a different demand for insulin in different menstrual cycle's phases and a higher insulin sensitivity at about 10.00 a.m. in luteal phase [17].

The number of studies concerning the influence of diabetes on sex hormones in normal menstrual cycle is limited. Zumoff and coleagues [18] noted no differences in cycle length, luteal phase length and periovulatory and luteal concentrations of gonadal steroids of diabetic women with normal menses and good glucose control compared to non-diabetic controls. However, they documented lower progesterone concentrations and higher oestradiol levels in the diabetics. Hyperandrogenaemia and normal free testosterone values, may also occur in type 1 diabetic women normally menstruating. Probably the worsened diabetes control may lead to increased SHBG (sex hormone binding globulin) levels through an increased production or decreased catabolism of this hepatic glycoprotein. Because free testosterone levels are normal, typical manifestations of hyperandrogenaemia, such as: hirsutism, obesity, irregularity menstruations or amenorrhea were absent [19].

Basal serum luteinizing-hormone (LH) and follicle-stimulating hormone (FSH) levels are usually normal in diabetic women with normal menstruation [10, 12]. However amenorrheic women have lower basal LH levels (fewer LH pulses and secretory episodes). Djursing [20, 21] documented a normal FSH response to gonadotropic releasing hormone (GnRH) despite low

plasma oestradiol levels in amenorrheic diabetic women but a diminished LH response. Grossman [22] suggest a normal LH response. South [23] noted an enhanced response of LH to GnRH, an observation similar to those noted in women with other amenorrheic states, such as anorexia nervosa and hyperprolactinaemia. Different reactions of luteinizing-hormone to GnRH suggest that menstrual disturbances in diabetic women may reflect abnormalities in a GnRH pulse generator in hypothalamus rather than primary pituitary dysfunction [10, 23, 24].

Also in type 1 diabetes mellitus lower basal prolactin levels were observed in women with or without amenorrhea. However, prolactin response to metoclopramide stimulation [dopamine antagonist] was decreased only in diabetic amenorrheic women [25]. These results suggest that increased central dopaminergic activity may be responsible for menstrual disturbances in diabetics via inhibition of GnRH secretion [26].

Many authors have investigated an influence of an impaired hypothalamic function on menstrual problems in women with diabetes. They suggest an abnormality in the GnRH pulse generator in hypothalamus [10]. In their research various hypothalamic neurotransmitters in order to define the mechanisms of GnRH pulse generator's destruction were used. Attention has been focused on the fact whether or not the activity of these neurotransmitters pathways is altered within the setting of diabetes. O'Hare [13] used naloxon which blocks central opioidergic activity and he found that hypogonadotropic amenorrhea characteristic for type 1 diabetes could not be attributed to increased opioidergic tone. Djursing and colleagues have proposed increased hypothalamic dopaminergic tone as a reason in the amenorrhea associated with diabetes. In their studies they have suggested that dopamine-associated suppression of GnRH pulse generator may play an etiological role in diabetic women amenorrhea as well as in other women with this dysfunction [8, 20, 25, 27, 28].

Despite more and more information about the causes and pathomechanisms of type 1 diabetic women's menstrual dysfunctions, problem is not defined clearly. Prelević compared hormonal profiles of two groups of diabetic amenorrheic women: first – with residual insulin and C-peptid secretion and classical hormone profile of the polycystic ovary syndrome (↑LH/FSH, ↑ testosteron, ↓ SHBG) and second – without endogenous beta cell and C-peptid activity (↓ LH, ↓ LH/FSH). Their results suggest that low LH amenorrhea seems to be a consequence of diabetes and is associated with a lack of residual insulin secretion. It is possible that insulin might be a neurotransmitter or neuromodulator within the brain thus regulating pituitary function [29].

Diabetes mellitus, just like other chronic diseases, may affect fertility. After introduction of insulin for the treatment of diabetes mellitus, most type 1 diabetic women are fertile [30]. Some of them have shorter fertile life because of delayed menarche and earlier menopause [31]. These women have a greater incidence of menstrual abnormalities, such as oligo- and amenorrhea, and in consequence fail to ovulate.

In medical literature an earlier menopause in type 1 diabetic women is described [11, 31]. Dorman et al. [31] suggest statistically significantly younger age of natural menopause for diabetics compared with non-diabetic sisters or controls. This study showed that diabetic women had on average 6 reproductive years less than healthy controls because of their older age at menarche and younger age at menopause. Prolonged hyperglycaemia and other long-term complications of the disease may be responsible. Early menopause may also have an autoimmune etiology. Strotmeyer et al. [11] defined mean age of natural menopause in diabetics as 42 years, however perimenopausal symptoms can be observed already in their thirties and forties. Earlier menopause may be caused by similar underlying etiological factors that predisposes these women to menstrual irregularities.

Despite common menstrual problems in diabetic women, infertility in this group occurs with the same frequency as in healthy women [7]. Gestation, despite introduction of a model of intensive insulin therapy and gradually better diabetic control, is still a problem for both obstetricians and diabetologists. Type 1 diabetes mellitus still carries an increased risk of gestational complications for mother and child [32, 33].

Until this time there is insufficient data on diabetic female sexual dysfunction. This problem has been described mostly in diabetic men and impaired sexual function in men is a well-documented complication of diabetes. Until 2000 fewer than 5 % of all publications about sexual dysfunction in diabetes concerned diabetic women. There may be some reasons for that disproportion: women and doctors may ignore this problem, female sexual dysfunction may be mistaken for depression, vaginal infections, urinary tract infections. In physiological terms, the female equivalent of male erectile dysfunctions is a reduced vasocongestion of the vulva and vagina, leading to impaired arousal and reduced vaginal lubrication [34].

Taking into account the young age of the group of women with sexual problems, the prevalence of sexual problems in this group is high. In the review of 25 years of research, Enzlin et al. [35] documented that the prevalence of impaired sexual arousal and inadequate lubrication was between 14 and 45% in diabetic women, significantly higher than in healthy women. There are no differences in other problems, such as: dyspareunia and problems with orgasm in both groups. Moreover, in a controlled study, comparing 120 women with diabetes and 180 non-diabetics, he demonstrated that significantly more women with diabetes (27%) than control subjects (15%) reported sexual dysfunctions [36]. Diabetic patients are at risk for neurological and vascular complications and psychological problems; investigators suggest that these pathologies may also reflect on sexual disturbances. In many studies concerning diabetic man there is a connection between neurological and vascular complications, psychological factors and erectile dysfunctions [37]. In a small num-

Table 1. Chronobiological parameters of urinary 6-sulfatoxymelatonin in breast-fed babies (n=8), their breast-feeding mothers (n=8), and formula-fed babies (n=8), and of tryptophan in breast milk (n=8).

Parameters	Mesor	Acrophase	Nadir
tryptophan (breast milk) µmol/l	67.95 µmol/l	03:00 h	15:00 h
6-sulfatoxymelatonin (natural) ng/ml	11.45 ng/ml	06:00 h	18:00 h
6-sulfatoxymelatonin (mathers) ng/ml	9.72 ng/ml	12:00 h	20:00 h
6-sulfatoxymelatonin (formula) ng/ml	9.82 ng/ml	12:00 h	00:00 h

Table 2. Comparison of the sleep parameters of breast-fed (n=8) and formula-fed (n=8) babies.

	Formula	Breast milk
Time in the crib	10h 2min ± 1h 10min	9h 54min ± 2h 36min
Assumed sleep	8h 53min ± 52min	9h 35min ± 41min [a]
Actual sleep	7h 7min ± 43min	8h 30min ± 49min [a]
Sleep efficiency	70.512 ± 5.78 %	81.45 ± 5.48 % [a]
Sleep latency	1h ± 45min	30min ± 17min

[a] $p<0.05$ with respect to the formula milk.

ber of studies about diabetic women the authors didn't find a clear relationship between sexual dysfunction and peripheral neuropathy [34, 35, 38]. Type 1 diabetic women with severe autonomic neuropathy can have an excellent sexual life, unlike men, so it is likely there are different predictors for sexual dysfunction in men and in women [39]. In Enzlin et al. [38] study, the largest ever done in the field of sexual function in diabetes, including 240 adult type 1 diabetic patients, sexual dysfunctions in men and in women were compared. They found, that more women without complications of diabetes have sexual problems in comparison to men without complications. More women than men reported depressive symptomatology. Their earlier study showed a greater incidence of depressive symptoms in diabetic women with sexual problems [36]. These results suggest that sexual dysfunction is predominantly related to psychological variables. The chronic course of diabetes and poor glycaemic control may influence the patient's mood and the incidence of depressive symptoms [16].

Vaginal infections, especially candidiasis- a common finding in diabetic women, can interfere with sexual intercourse. Severe infection can be very irritating and painful and cause a re-infection. It occurs most often if the blood glucose control is poor.

Urinary tract infection (UTI) also have an effect on reproductive period in diabetic women. In the recent years more authors try to explain whether that problem is more frequent in diabetics compared to healthy women. It could be result of a different definition of bacteriuria and infection, methods of investigations and selection of a patient's group. No differences in earlier publications was found between a frequency of these problems in young diabetic women compared to controls [40], but recent studies documented two or threefold increase of UTI in diabetic patients [41]. Asymptomatic bacteriuria occurs in long-lasting diabetes mellitus in about 12% to 26% [42]. Symptomatic UTI are also frequently seen in diabetics but still under diagnosed. Upper UTI can result in a number of severe complications, such as: intrarenal abscess, perinephric abscess, papillary necrosis, sepsis. Asymptomatic bacteriuria does not exclude upper urinary tract involvement, especially involvement of the kidney [43].

Possible reasons for the increased incidence of UTI include the presence of diabetic autonomic neuropathy causing functional bladder dysfunction, coexisting vaginitis, nephropathy as a result of diabetic microangiopathy, previous urological procedures [44]. However, only a part of them concerns of type 1 diabetic women in reproductive period. Geerling et al. [45] did not observe that poor regulation of diabetes or the presence of diabetic cystopathy, neuropathy, macroalbuminuria and bacteriuria increased the risk of UTI development. Independent risk factors for the development of UTI include sexual intercourse. They noted that the presence of macrovascular complications was inversely correlated with the risk of development of UTI. The authors tried to explain that finding by a negative influence of macrovascular complication on sexual life in diabetics. They also showed that glucosuria was not a risk factor of asymptomatic bacteriuria or the development of symptomatic UTI, despite the fact that glucosuria enhanced bacterial growth in vitro [46]. It could be a result of differences between the conditions in vitro (growth during 6 hours) and in vivo (micturition every 4–6 hours).

Urinary incontinence is also a urinary tract problem in diabetic patients. Diabetes mellitus next to: pregnancy, hormonal variation, menopause and other chronic diseases (multiple sclerosis, stroke) is more often considered a risk factor of urinary incontinence [47, 48]. In the middle aged people and in the elderly there is an increasing prevalence of urinary incontinence [48]. Diabetes, is estimated to account for 30% to 70% of increased risk of urinary incontinence in women [47]. Mechanisms by which diabetes might promote incontinence are not clear. The most likely causes are microvascular complications leading to a damage to vascular and neurological innervation of the urethral

sphincter and bladder [49]. Until now there are a few small studies about an influence of diabetes mellitus on urinary incontinence. Unfortunately, most of them did not differentiate type 1 and type 2 diabetes and these studies were done among elderly patients with diabetes. And because of that this problem requires more investigations.

It has been shown in the above literature review that disturbances of the reproductive system affect somatic, psychological and social dimension of life for women with diabetes. The number of reports concerning this problem, however small, has been increasing systematically over recent years. This fact shows that both the patients and doctors as well as governing institutions started to appreciate the importance of these problems which may influence the scientific research in academic centers.

Better understanding of the care of these disturbances will lead to the improvement of diabetological and obstetrical care. Also more efficient prophylaxis is being implemented. This fact helps to lower the incidence of infertility and unsuccessful pregnancies. It also improves the diabetic women's health and allows for hopeful outlook for future successful research which may improve the situation of women with diabetes.

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