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The Interaction Between the Female Reproductive System and Type 1 Diabetes

Coons A[1] and Shubrook JH[2]*

[1]*Master of Science in Medical Health Sciences Program, Touro University California, USA*

[2]*Department Primary Care, Touro University California, USA*

Abstract

Not much is known about how the female reproductive system and blood glucose (BG) control are related in Type 1 Diabetes (T1D). Studies show that women frequently struggle to achieve glycemic control of their diabetes compared to men. The purpose of this review is to describe what is known about the interaction between the female reproductive system, ovarian sex hormones, and blood glucose in people with T1D. This literature review includes data collected from the spring of 2018 to May 20th, 2021 and includes 69 papers. Data were found through search engines including PubMed, Scopus, Google Scholar, and Google. Data were filtered by English-only and human-only studies as well as the date range "since 2017" for studies on technology. T1D may put females at risk of ovarian hyperandrogenism and other reproductive abnormalities. About 25% of women with type 1 diabetes have menstrual cycle irregularities. Among studies that compared glucose control during the different phases of the menstrual cycle, there is a consensus that for at least a subset of women with T1D, the luteal phase is a time of either increased blood glucose, increased insulin dosage needs, and/or increased insulin resistance. More research should be done on this topic, including research to create individualized algorithms for determining insulin dosage adjustments based on personal hormone levels to be used during puberty, across the menstrual cycle, and during menopause.

Keywords: Type 1 diabetes; Menstrual cycles; Reproductive abnormalities; Hyperandrogenism; Insulin resistance

Abbreviations

T1D: Type 1 Diabetes; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; DHEA: Dehydroepiandrosterone; PCOS: Polycystic Ovary Syndrome; PCOM: Polycystic Ovary Morphology; PMS: Premenstrual Syndrome; ALLO: Allopregnanolone; SSRIs: Selective Serotonin Reuptake Inhibitors; CGM: Continuous Glucose Monitor; HbA1c: Hemoglobin A1c; Mg/dL: Milligrams/Deciliter; BG: Blood Glucose

Introduction

Not much is known about how the menstrual cycle and blood glucose are related in Type 1 Diabetes (T1D). There is evidence that ovarian sex hormones and blood glucose (BG) levels have a bidirectional relationship [1,2]. Research shows that uncontrolled T1D is associated with reproductive system abnormalities [3,4]. However, research also supports that excess exogenous insulin used in the attempt to reach optimal blood glucose levels is associated with abnormalities of the female reproductive system as well [5].

Many menstruating women actively adjust their insulin at different menstrual cycle phases [6]. One study that evaluated self-reported blood glucose changes and insulin dosage adjustments in females with T1D found that 61% of females with T1D noticed menstrual cycle fluctuations in blood glucose, and 36% adjusted their insulin accordingly [7] (Figure 1). Furthermore, anecdotal evidence shows that many physicians advise their menstruating patients to match their blood glucose levels to the phase of their menstrual cycle and to adjust their insulin accordingly [8,9]. However, there is not a standardized algorithm agreed upon to assist patients to adjust insulin during the different phases of the menstrual cycle. Additionally, this medical advice is under the assumption that the patient has a regular menstrual cycle and/or regular cyclical patterns of blood glucose levels corresponding to the menstrual cycle. About 25% of women with T1D have menstrual cycle irregularities [1,5,10-12]. Menstrual cycle irregularities have been shown to increase the risk of coronary artery disease [13]. The severity of this issue is made evident by one study that showed that in 53 occurrences of

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Correspondence:
Aisha Coons, Master of Science in Medical Health Sciences Program, Touro University California, 1310 Club Dr, Vallejo, CA 94592, USA, E-mail: acoons@student.touro.edu

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diabetic ketoacidosis in the females, over half were associated with menstruation [14].

Studies show that women frequently have inadequate control of their diabetes compared to men [14-17]. One study showed that women with T1D had a two times higher excess risk of fatal and nonfatal cardiovascular events compared to men with T1D [18]. Among women with T1D, the all-cause mortality excess risk was 40% greater compared to men with T1D [18]. The purpose of this review is to describe what is known about the interaction between the reproductive system of menstruating people, ovarian sex hormones, and blood glucose in people with T1D.

Methods

This literature review includes data collected from the spring of 2018 to May 20th, 2021 and includes 69 papers. Data was found through search engines including PubMed, Scopus, Google Scholar, and Google. Some search terms included were "insulin sensitivity and premenstrual syndrome," "progesterone and insulin resistance," and "insulin requirements and the menstrual cycle." Only papers in English were included. When researching certain topics such as technology, search terms were filtered by the date range "since 2017." Research articles done on animals were excluded so that this review would be relevant to humans.

Results

Menstrual cycle hormones and insulin resistance

The menstrual cycle is known to be controlled by at least four main hormones, including progesterone, estrogen, luteinizing hormone, and follicle stimulating hormone. Progesterone has been shown to cause insulin resistance [19-21]. While some research shows that estrogen increases insulin resistance [19,22], other research shows that estrogen decreases insulin resistance [23-25]. Two other major hormones, Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) are known to affect the menstrual cycle. When human granulosa cells are stimulated by both insulin and FSH together, they have been shown to increase progesterone secretions [26]. Additionally, insulin has been shown to increase basal production of estrogen, progesterone, LH, and LH-stimulated steroids in granulosa cell cultures [26]. However, as Goldner et al. [27] point out, females with T1D often administer insulin when their blood glucose levels are high [27], which occurs often for many females with T1D in the luteal phase when progesterone is high [6,27,28].

Research on how androgens such as testosterone affect insulin resistance across the menstrual cycle is also unclear. Research shows that the ratio of testosterone/estradiol is constant throughout the menstrual cycle in young healthy females [29], and the levels of testosterone fluctuate cyclically throughout the menstrual cycle [29,30]. In healthy women, menstrual cycle variation in baseline testosterone concentration has been shown to be correlated with testosterone and cortisol reactivity to stressors [31]. There is not a consensus in the research on how androgens including testosterone affect insulin resistance [32-34]. However, the ratio of Dehydroepiandrosterone (DHEA)/testosterone has been shown to be more correlated to insulin sensitivity than to DHEA or testosterone alone [32].

Reproductive abnormalities

A review on puberty in females with T1D by Codner et al. [1] explains that although the major advances in (T1D) have led to benefits of intensive insulin treatment in managing this disease, excess exogenous insulin therapy has been associated with less desirable effects on other organs such as the ovaries [1,5]. This is because subcutaneously administered insulin does not have the first pass effect from the liver that endogenous insulin has [1,35,36]. This results in under-insulinization of the liver, over-insulinization of the rest of the body, and may result in undesirable effects on organs [1,35,36].

Testosterone and testosterone/sex-steroid-binding plasma protein ratio increases in early puberty in healthy females [37,38]. By the end of puberty, Codner et al. [39] found that compared to controls, females with T1D have higher stimulated testosterone and 17-OH progesterone levels, which they reason is most likely due to the development of ovarian hyper-androgenism [5,39]. However, hyperandrogenism can be from the adrenal glands as well [40]. Women with T1D and without amenorrhea have been shown to have hyperandrogenism with intensive insulin treatment [41]. Notably, women can still bleed even though they did not ovulate in the previous cycle [42]. Hyperandrogenism in women with T1D has been shown not to depend on the total daily amount of insulin used [43]. Escobar-Morreale et al. [43] found that 38.8% of the 85 participants in their study presented with hyperandrogenic disorders [43].

Studies show that there is some delay in the age of thelarche, pubarche, and menarche in girls with T1D [10,44,45]. The frequency of menstrual irregularities in adolescents with T1D has been shown to be higher (54%) than in healthy girls (21%) and is also associated with worse metabolic control and weight gain [3]. Adult women with T1D have a significantly higher risk of having menstrual disorders compared to healthy women, and about 25% of women with T1D have menstrual cycle irregularities [1,5,10-12].

Menstrual cycle irregularities increase the risk of coronary artery disease [13]. Codner et al. [5] found that women with T1D have an increased risk of developing Polycystic Ovary Syndrome (PCOS) with a relative risk of 15.4 [5]. They also found that PCOM (Polycystic Ovary Morphology) was present in 54.8% of the women with T1D that they studied. PCOS can be defined as a syndrome of ovarian dysfunction as well as hyperandrogenism and polycystic ovary morphology based on the Rotterdam criteria [46]. It is also associated with menstrual cycle irregularities, insulin resistance, and cardiovascular events [46]. There are also differences in PCOS of women with T1D compared to non-diabetic women including there being normal sex hormone binding protein in women with T1D and PCOS [43,47]. Women with T1D and PCOS have also been shown to have normal levels of DHEA-sulfate [43]. However, children with T1D have been shown to have higher DHEA than normal [40]. PCOS may consequently be under diagnosed in women with T1D [1].

The menstrual cycle and cyclical fluctuations of glucose metabolism in insulin-dependent diabetes

Even before the first menstruation begins in young girls with diabetes, cyclical fluctuations in blood glucose can be seen in response to hormonal fluctuations, as shown in a series of case studies [48]. The mean age at which this occurred in the participants was 10.8 years. However, this study suggests that changes could begin around 9 years of age.

Multiple quantitative studies have tried to evaluate how the menstrual cycle affects diabetes management in females with insulin dependent diabetes (Table 1). These studies that explored the

Table 1: Quantitative results of studies evaluating diabetes indicators across the menstrual cycle in women with insulin dependent diabetes mellitus.

Authors	Methods: Number of participants; Number of menstrual cycles evaluated	Diabetes control indicators used; Any indication of worse BG control during the luteal phase?	Pattern of menstrual cycle hormone levels	Pattern of food intake
Widom et al. [49]	16; 1	Glucose Metabolism (hyperglycemic, hyperinsulinemic clamp studies); Yes (in a subset of participants)	Subset of participants with decreased glucose metabolism and a significant rise in serum estradiol levels in the luteal phase.	N/A
Lundman et al. [6]	20 (and 20 controls); 2	BG Levels, Extra Insulin Injected, and Glycated Hemoglobin; Yes (glycated hemoglobin)	N/A	There was no increase in mean food intake in the participants with T1D.
Lunt and Brown [7]	124; N/A	Glycated Hemoglobin; N/A	N/A	N/A
Goldner et al. [27]	4; 3	BG Levels; Yes (in a subset of participants)	Progesterone, but not estrogen levels were similar in all 4 subjects.	N/A
Brown et al. [28]	12; 3	BG Levels; Yes (as well as during periovulation)	Hormone levels followed expected patterns.	Total daily carbohydrates or calories did not fluctuate significantly.

Abbreviations: T1D: Type 1 Diabetes; N/A: Not Applicable; BG: Blood glucose

menstrual cycle phases and fluctuating blood glucose levels, insulin needs, and/or insulin resistance in females with insulin-dependent diabetes exclude women with irregular menstrual cycles [6,27,28,49]. Several studies have found that there is just a subset of women with insulin-dependent diabetes that seem to have menstrual cycle-related blood glucose patterns [7,27,28,49,50]. Multiple quantitative studies demonstrate that other factors besides nutrient intake contribute to fluctuations in blood glucose control across the menstrual cycle [6,28]. Among studies that quantitatively compared glucose control during the different phases of the menstrual cycle, there is a consensus that for at least a subset of women with T1D, the luteal phase is a time of either increased blood glucose, increased insulin dosage needs, and/or increased insulin resistance [6,27,28,49].

The amount of hormones secreted has been shown to affect blood glucose as well (Table 1). For example, a study by Widom et al. [49] showed that women with higher levels of estrogen during the luteal phase showed less insulin sensitivity during that period compared to women that had the same amount of estrogen during both the follicular and luteal phases. Widom et al. [49] also evaluated testosterone levels along with other hormones. Although it was not significantly lower, the group of 7 participants with less glucose metabolism during the luteal phase also had lower testosterone compared to the group of 9 women that had greater glucose metabolism. Additionally, a study by Goldner et al. [27] evaluated blood glucose levels during the different phases of the menstrual cycle as well as the product of the average daily glucose times the insulin dosages during a 24-h day compared to a day in the menstrual cycle. This calculation was similar to the homeostasis model assessment and was completed to account for the necessity of correction boluses of insulin for higher blood glucose levels [27,51]. They found that the pattern of progesterone levels was similar in all four of their subjects, but the pattern of estrogen levels was not similar. In one of the four subjects, there was an inverse correlation between the level of estrogen and blood glucose levels above 140 mg/dL [27].

Lunt and Brown [7] studied the reported premenstrual changes in glycemic control and insulin requirements in people with T1D. They collected qualitative data by surveying 124 women with T1D between 18 and 40 years old. The answers from the questionnaires showed that 61% of women noticed fluctuations in capillary blood glucose levels at or around the time of menstruation (Figure 1). Over 1/3 (36%) adjusted their insulin accordingly. Two-thirds (67%) of participants taking the birth control pill (containing estrogen/progesterone) noticed changes in blood glucose at or around their time of menstruation. Seventy-one percent of the respondents that noted changes in appetite also noticed menstrual cycle-related changes in blood glucose levels. Almost half (49%) of respondents that did not notice changes in appetite noticed changes in menstrual cycle-related blood glucose levels. It is worth noting that people with T1D and optimal BG control frequently have more accurate carbohydrate (carb)/insulin ratios or nutrient/insulin ratios as well as correction factors compared to people that have suboptimal BG control [52,53].

Lunt and Brown also tested the participants' glycated hemoglobin (Table 1) [7]. The mean glycated hemoglobin of the participants making premenstrual changes in insulin dosage was not significantly different from that of the participants not making premenstrual changes in insulin dosage. The researchers concluded that based on their study, there was no evidence to show that the adjustments in insulin dosage improved glycemic control in this population. However, short term glycemic control measurements such as time in range from continuous glucose monitors have been shown to be negatively correlated with complications such as painful diabetic neuropathy after adjusting for glycated hemoglobin, glycemic variability indicators, and other risk factors [54,55].

Some researchers suggest that Premenstrual Syndrome (PMS) may cause cyclical disturbances in blood glucose in a subset of women with insulin-dependent diabetes [2,50]. Cawood et al. [50] collected qualitative data by surveying 406 women with insulin-dependent diabetes [50]. This study found that women with insulin-dependent diabetes that reported (PMS) more commonly noticed blood glucose or urine glucose levels changed in a menstrual cycle-related pattern compared to those that did not report PMS. In a review by Trout and Teff, they suggest that the conflicting results that they found of studies on insulin requirements and T1D during the menstrual cycle may be due to the inability of some women but not all women to convert progesterone to Allopregnanolone (ALLO) [2,56]. Progesterone has been shown to significantly increase serum ALLO and alter amygdala activity in healthy women [57]. One study of 46 women with PMS who were otherwise healthy were studied to see if Selective Serotonin Reuptake Inhibitors (SSRIs) would help [58]. They found that when the baseline ALLO levels were low, SSRIs increased their ALLO levels and improved dysphoric symptoms. Additionally, certain SSRIs have been shown to lower fasting blood glucose in non-diabetic patients with major depressive disorder [59].

Menopause and T1D

A longitudinal study showed that as women go through menopause, their testosterone levels remain stable, but their estrogen declines [60]. Another study showed that for non-diabetic women

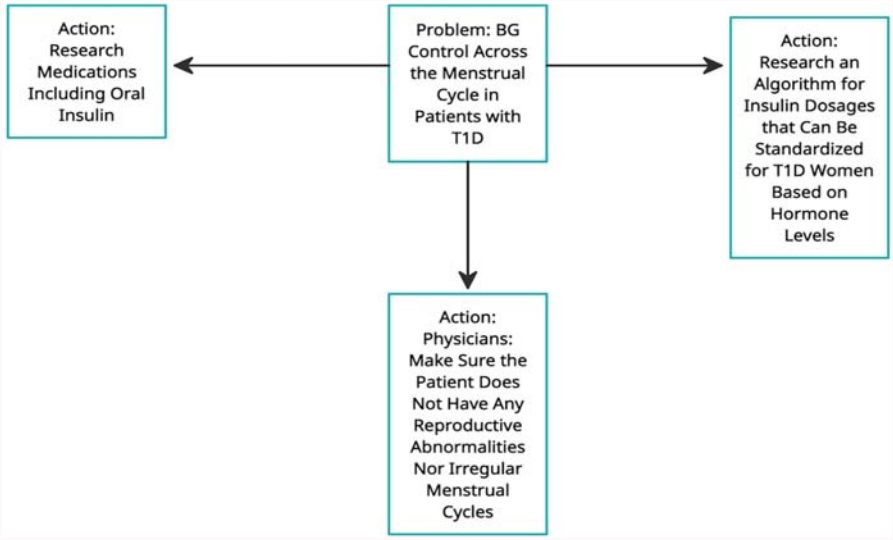

Figure 1: A problem for females with T1D is blood glucose control throughout the menstrual cycle. Here are 3 ways to act.

of various ethnicities, baseline total testosterone/estrogen ratio as well as its rate of change were associated with increased occurrence of metabolic syndrome during the menopausal transition [61]. Baseline estradiol and change in estradiol were not associated with the occurrence of metabolic syndrome. They concluded that it is the interaction between testosterone and estrogen that is a risk factor for developing metabolic syndrome during the menopausal transition. It is worth noting that women with T1D have been shown to have an increased prevalence of hyperandrogenism beginning in puberty and continuing throughout their reproductive age [5,39-41,43].

Studies show that women with T1D are more likely to have earlier menopause [10,45,62]. In fact, studies show that women with T1D have shorter reproductive durations as well [10,45,62]. Early natural menopause has been found to be associated with increased all-cause mortality and ischemic heart disease mortality [63]. Additionally, Dorman et al. [45] found that younger age at onset of T1D was associated with early menopause. HbA1c and insulin used per day were the same between women with T1D that had early menopause and women with T1D that had later menopause.

Potential medical interventions

Kurzthaler et al. [64] studied 19 women with PCOS and found that metformin decreased serum concentration of LH-stimulated testosterone [64]. In addition, metformin is thought to work by increasing the sensitivity of the liver to insulin and has been shown to decrease basal glucose concentrations in people with Type 2 Diabetes (T2D) [65]. Used in patients with T1D, metformin use over a year has been shown to decrease plasma glucose concentrations, reduce metabolic syndrome, and reduce insulin needs more than insulin alone [66]. Additionally, this study showed that when metformin was used with insulin over a year, the average weight of the participants did not increase, while insulin use alone showed an increase in the average weight among the participants [66]. One study evaluated if metformin was useful in treating hyperandrogenism in females with T1D [67]. The results were that the serum androgens decreased significantly compared to placebo, but it did not affect other clinical parameters.

Other medications have been studied as well. Anti-androgen drugs have also been shown to decrease insulin resistance [34]. It is known that oral medications enter the bloodstream through the small intestines, and therefore it directly goes to the liver before the rest of the body. Oral insulin has the first pass effect through the liver [68,69], unlike subcutaneous insulin in use today [1,36]. Strotmeyer et al. [10] found that oral contraceptives helped prevent menstrual cycle problems for women 30 to 39 years of age [10]. As mentioned above, SSRIs have been shown to lower fasting blood glucose in non-diabetic patients with major depressive disorder [59].

Discussion and Conclusion

Anecdotally, those who menstruate are often told by their physicians to match their blood glucose levels to the phase or time of their menstrual cycle [8,9] (Figure 1). However, this advice may not be the most helpful response to menstruating patients with T1D, who are more likely to have irregular menstrual cycles and early menopause [5,10-12,45,62]. Additionally, there is not a standard treatment plan for menstruating people with T1D in terms of by what percentage they should adjust their insulin dosages and when throughout the menstrual cycle. Research shows that uncontrolled T1D is associated with reproductive system abnormalities [3,4]. However, research also shows that excess insulin used in the attempt to reach optimal blood glucose levels is associated with abnormalities of the female reproductive system as well [5]. Females are having more diabetes related complications and death than males with diabetes [18]. It is crucial to try to find alternative strategies to help menstruating people with T1D.

There is a consensus among the research that the luteal phase is a time of increased insulin resistance, increased insulin dosages, and/or increased blood glucose for at least a subset of women with T1D [6,7,27,28,49]. There is also a consensus that progesterone, which is known to be highest during the luteal phase, is associated with insulin resistance [19-21], but there is not a consensus for the effect of estrogen on insulin resistance [19,22-24]. The ratio of testosterone/estradiol is constant throughout the menstrual cycle in young healthy females [29], and the levels of testosterone fluctuate cyclically throughout the menstrual cycle [29,30]. There is not a consensus in the research on how androgens including testosterone affect insulin resistance [32-

34]. However, the ratio of DHEA/testosterone has been shown to be more correlated to insulin sensitivity than to DHEA or testosterone alone [32]. Furthermore, women with T1D have been shown to have an increased prevalence of hyperandrogenism beginning in puberty and continuing throughout their reproductive age [5,37-41,43]. Therefore, it may be worth researching testosterone as a ratio of both estrogen and DHEA and how it may affect insulin resistance in women with T1D. Additionally, as Figure 1 shows, studies should be done to create an algorithm for personalized insulin adjustments to be used during puberty, across the menstrual cycle, and during menopause based on personal reproductive hormone levels.

There is a great need to find different methods used to study T1D and the menstrual cycle. For example, there is evidence that only a subset of women with T1D notice blood glucose changes throughout their cycles [7,27,28,49,50], so group studies might not show patterns that some, but not all females may notice [2,6]. Insulin and blood glucose levels should not be studied separately. Additionally, studies should evaluate periovulation separately in addition to the luteal phase and the follicular phase, such as was done in the study by Brown et al. [28]. Studies should also be done to determine if carb/insulin or nutrient/insulin ratios are more accurate at certain phases of the menstrual cycle than at others in a controlled setting where food intake and blood glucose can be monitored. People with T1D and optimal BG control frequently have more accurate carb/insulin ratios or nutrient/insulin ratios as well as correction factors compared to people that have suboptimal BG control [52,53]. Additionally, studies should not only use long-term blood glucose control indicators such as HbA1c, but also short-term blood glucose control indicators as well now that real time continuous glucose monitors are widely available. Short term glycemic control measurements such as time in range from continuous glucose monitors have been shown to be negatively correlated with complications such as painful diabetic neuropathy after adjusting for glycated hemoglobin, glycemic variability indicators, and other risk factors [54,55]. Additionally, research should be done to assess whether irregular menstrual cycles more likely leads to irregular blood glucose management in women with T1D, considering that females with T1D are predisposed to having irregular menstrual cycles [5,10-12,45].

Further research is needed on medications, as shown in Figure 1, such as oral insulin, metformin, antiandrogen medications, oral contraceptives, and SSRIs since they may be beneficial for people with diabetes, for lowering blood glucose levels, and/or insulin resistance. There should also be studies to determine if there are screening mechanisms that can help identify if females have irregular blood glucose fluctuations across the menstrual cycle due to reproductive abnormalities and/or perimenopause/menopause. For example, perhaps physicians can screen women with T1D by asking them when they were diagnosed with T1D since studies show that the age of onset of T1D is associated with early onset of menopause [45].

Insulin dosages and HbA1cs may not be appropriate screening criteria for whether menstruating people with T1D might have reproductive abnormalities and/or early menopause. Dorman et al. [45] found that HbA1c and insulin used per day were the same between women with T1D that had early menopause and women with T1D that had later menopause [45]. Some studies show that reproductive abnormalities in females with T1D are not associated with the amount of subcutaneous insulin taken [43,45]. Physicians may also want to consider screening their menstruating patients with T1D for reproductive abnormalities, as shown in Figure 1, such as by ordering appropriate tests considering the high prevalence of reproductive abnormalities in females with T1D [1,3,5,10-12,39,41,43,45,62].

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