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Ovarian Aging in Women with Diabetes: An Overview

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Abstract

Type 2 diabetes is a global epidemic, and the prevalence and incidence of type 1 diabetes are increasing. The negative effects of diabetes on kidneys, nerves, and vessels are well established. The effect of diabetes on reproductive function is less well understood, but important to characterize, given the increasing numbers of young women with diabetes. In this review, we summarize the available literature on how women with diabetes experience ovarian aging, from menarche to menopause. We report that women with type 1 diabetes appear more likely to have ovarian dysfunction, manifested by delayed menses, menstrual irregularities, and possibly earlier menopause. Studies of women with type 2 diabetes are inconsistent but suggest increased anovulation and earlier menopause. Differences in reproductive aging between women with type 1 and type 2 diabetes raise questions about potential differences in the mechanisms contributing to ovarian aging. Although there is shared glycemic dysregulation, fundamental differences in insulin presence and processing distinguish the two diseases. This review suggests that insulin, age at diagnosis, and weight play a role in ovarian dysfunction. More long-term studies are needed to evaluate the multitude of factors that may disrupt hypothalamic, pituitary, and ovarian function in women with diabetes.

Keywords

gonadal aging; ovarian aging; reproductive health; diabetes; menopause; menarche

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Contributors

MFW oversaw the systematic literature search, revision of the manuscript, final manuscript preparation and submission.

JJM performed the first literature search, drafted the initial manuscript and revised the manuscript.

CK revised the manuscript, and oversaw final manuscript preparation and submission.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Introduction

In the United States, more than 11% of women over 20 years of age have diabetes[1]. Among girls born in the year 2000, more than 1 in every 3 are expected to develop diabetes in their lifetime[2]. In recent years, more women of childbearing age have been diagnosed with diabetes, raising alarm about the need for more information on harms of diabetes on reproductive health[3]. Information on age-related changes in ovarian function, or ovarian aging, is also needed because women, both with and without diabetes, are more often choosing to have children at later ages.

The average worldwide life expectancy increased by 5 years from 2010 to 2015 and is now 73.8 years for women [4]. As the time lived with diabetes increases, understanding the unique reproductive trajectories of women with this chronic disease becomes increasingly important [5]. It is well documented that early ovarian aging is associated with acceleration of bone loss and higher risk of cardiovascular disease[6]. Since women with diabetes are at higher risk for bone disorders as well as cardiovascular disease, identifying patterns of reproductive aging could improve identification of those at highest risk for these chronic conditions. Although the mechanisms underpinning the decline of ovarian reserve in healthy women have not been studied extensively, recent discoveries regarding endocrine, metabolic, and genetic factors are leading to a better understanding of this complex phenomenon[5]. This manuscript summarized a systematic search of the literature on how women with diabetes experience the continuum of ovarian aging, from menarche through menopause. It also emphasizes the need for more work on this increasingly relevant topic.

Methods

A systematic search of the literature was performed by a medical research librarian (P.W.) and led to the identification of 82 articles. The search was performed in MEDLINE (1966 to December August 2016) and EMBASE (1980 to August 2016). For diabetes, the medical subject headings (MeSH) and text terms included: diabetics; diabetic patients; Diabetes Mellitus; Diabetes Mellitus, Type 2; Diabetes Mellitus, Type 1; Diabetes Complications; diabetes mellitus type 1; diabetes mellitus type 2; insulin dependent diabetes mellitus; non insulin dependent diabetes mellitus. These diabetes MeSH and terms were combined with female reproductive aging MeSH and text terms: puberty, menarche, menopause, menopause, premature, premenopause, perimenopause, postmenopause, climacteric, gonads, reproductive aging, ovarian aging, ovarian function, ovarian reserve, gonadal aging, and gonads. The search was limited to studies of women ("women" or "female") and to epidemiologic studies ("epidemiologic studies"; "cohort studies"; "case control studies"; or "cross sectional studies"). Studies of complications of diabetes were avoided (NOT "cardiovascular", "cardiac", "cancer", "angina", "stroke").

Inclusion in final sample of manuscripts

Approximately 80 manuscripts were identified initially through the systematic search. Individual abstracts were reviewed by the senior author (M.W.). The final sample was limited to manuscripts focused on women with existing diabetes rather than studies of diabetes as a covariate (~30% of exclusion of manuscripts was for this reason). Manuscripts

regarding sexual health, medical complications of diabetes, pregnancy issues including lactation and gestational diabetes, and menopausal symptoms were excluded. After review of the remaining manuscripts (n~30) and their bibliographies, additional articles identified were added at the discretion of the authors.

Results/Discussion

Type 1 Diabetes Mellitus (T1DM)

Menarche in Women with T1DM—Modern treatment of diabetes has improved the lifespan—and in turn the reproductive lifespan—of girls and women with this disease. Prior to the advent of insulin therapy, girls with T1DM menstruated rarely [7, 8]. Since that time, the majority of reports suggest that girls with T1DM have later onset of menarche than girls without this disorder (Table 1). The Pittsburgh Familial Autoimmune and Diabetes (FAD) Study reported that women with T1DM had later age at menarche compared to sisters without DM or unrelated controls[9]. Studies from Colorado [10, 11] and other countries (Table 1) report similar findings [12–16]. Most of these studies as well as a study by Kjaer et al[7] suggest that T1DM is associated with delay in menarche especially when diabetes is diagnosed before menarche, rather than after. In support of this hypothesis, duration of diabetes is positively correlated with age at menarche [10, 14, 17, 18].

Age at menarche has decreased over time among girls with and without diabetes [11, 19]. For girls with diabetes, it is possible that improved glycemic control has caused this decline in age at menarche. Alternatively, it is possible that factors contributing to earlier age at menarche for all girls, including obesity, have reduced the impact of diabetes upon age at menarche. Of note, glucose control, as reflected by hemoglobin A1C (HbA1C), is inconsistently associated with delay in menarche. Rohrer et al found that a 1% increase in HbA1C resulted in a 0.07 year delay in menarche[17]. However, Schweiger et al found no correlation between HbA1c and menarche ($r = 0.01$, $p = 0.91$)[10], and Picardi et al also observed that even among girls with well controlled diabetes (mean HA1C <7.5%), age at menarche was still delayed[14]. This suggests that processes other than hyperglycemia may drive the delayed age at menarche observed in girls with T1DM. The significant period of weight loss and physiologic stress preceding the diagnosis of T1DM is one possible mechanism[7].

Reproductive Years in T1DM

Menstrual cycle characteristics in women with T1DM: Menstrual irregularities, including amenorrhea, oligomenorrhea, and menorrhagia, are more common in women with T1DM compared to women without diabetes. Kjaer et al noted that 22% of women with T1DM compared to 11% of women without diabetes reported menstrual dysfunction ($p=0.02$) [7]. These differences were even more pronounced when diabetes occurred before puberty. In a cohort of Polish women, Yeshaya et al noted that amenorrhea was twice as common in women with a very early onset of T1DM (in early childhood) as compared with women with onset of T1DM after menarche (44% versus 21%; $p=0.05$) and was more common in women with complications of T1DM as compared to those without (43% versus 33%; $p=0.05$) [18].

The FAD study found that women with T1DM were more likely to have menstrual irregularities before 30 years of age compared with sisters without diabetes or unrelated controls (46%, 33%, and 33%, respectively, $p = 0.04$). The FAD study also found an overall 6-year reduction in the number of reproductive years (time between age at menarche and menopause) (30.0, 37.0, and 35.2 years, respectively, $P = 0.05$) in T1DM[9]. This decrease raises concerns that women with T1DM may have a lower ovarian reserve and diminished reproductive potential.

Ovarian Reserve in Women with T1DM: Ovarian reserve is the estimate of the remaining follicle pool in a woman's ovaries. Theoretically, ovarian reserve is fixed at birth[20], and thus depletion of follicles early in the life course will result in lower follicle numbers later in reproductive life. As exogenous insulin use can stimulate maturation of the ovarian follicle, or folliculogenesis, women with T1DM may be predisposed to develop excessive numbers of follicles early in life. Theoretically, this stimulation could lead to depletion of the endogenous follicular pool and earlier ovarian failure compared to women without diabetes. Tools for assessing ovarian reserve include follicle stimulating hormone (FSH), anti-Mullerian hormone (AMH), and antral follicle count (AFC), and low ovarian volume with high FSH, low AMH, and low AFC/low volume suggesting low ovarian reserve.

Several reports support a greater degree of follicle development in women with T1DM compared to controls. Codner et al recruited a sample of 56 Chilean girls with T1DM and matched them by pubertal stage with healthy girls recruited from the community for a study of ovarian morphology and function. Ovarian volume was consistently higher in girls with T1DM among all Tanner stages as compared with controls (ANCOVA $p < 0.05$)[21]. Codner next performed a case ($n=48$)-control ($n=36$) study of ovarian morphology of young women (ages 15–40) with T1DM. They again observed significantly larger ovaries among women with T1DM compared with controls (9.3ml versus 7.1 ml; $p < 0.01$). They also observed more women with AFC ≥ 12 (a criteria for polycystic ovaries) (36% vs. 11%; $p < 0.01$) and found an association between intensive insulin use and the presence of polycystic ovarian morphology[22]. Consistent with this observation, Miyoshi et al saw a 52% prevalence of polycystic ovarian morphology (≥ 10 AFC) in a sample of 21 Japanese women with T1DM[23].

Consistent with the hypothesis of follicular depletion, Soto et al assessed ovarian reserve in women in later reproductive age, and found that AMH levels were lower in women with diabetes as compared with controls (4.1 versus 9.5pmol/l, $p=0.006$), suggesting a smaller ovarian follicle pool among women with T1DM as they approached menopause[24]. However, not all studies have reported patterns of early follicular development followed by later follicular decline. In a comparison of women with and without T1DM, Kim et al found that women with T1DM had lower AMH concentrations than age-matched counterparts initially, but concentrations were similar in later reproductive age[25]. This suggests that T1DM may negatively affect reserve, but in earlier rather than in later reproductive years. In multivariable modeling, neither diabetes duration ($p=0.86$), time-weighted HbA1C ($p=0.34$), nor time-weighted insulin dose ($p=0.73$) were associated with change in AMH level over time [26]. This suggests that ovarian reserve declines similarly in women with T1DM, regardless of the severity of glucose derangement and the aggressiveness of diabetes

treatment. Thus, in the modern era of diabetes treatment and management, tighter diabetes control may have little effect on ovarian reserve in mid-life women. However, this may not be true for younger women with diabetes or those with poorer control. Further study is needed to elucidate ovarian aging in women with T1DM in this age group and reconcile the inconsistencies in ovarian aging measures (e.g. high AFC and low AMH) observed by others[21–24].

Menopause in T1DM—Given the mixed data on ovarian reserve in women with T1DM, studies of the timing of menopause could provide insight into the potential presence of earlier or even later reproductive aging in these women. However, few studies examine this topic and have not found strong associations between T1DM and age at menopause. Using data from the FAD study, Dorman et al reported a younger age at menopause among women with T1DM as compared with their sisters and healthy controls (41.6, 49.9, and 48.0 years, respectively; $p=0.05$)[9]. Severity of T1DM could contribute to an earlier menopause. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the mean age of menopause was 52.0 among 258,898 women. Among those diagnosed with diabetes before age 20 (presumed T1DM) menopause occurred significantly earlier[3]. However, more recent studies note no difference in age at menopause in women with and without T1DM. Sjoberg et al reported the cessation of menses as occurring at age 52.5 years among a sample of Finnish women with T1DM, an age not younger than the age at menopause of the average Finnish population (median 51 years)[27]. The Ovarian Ageing in Type 1 Diabetes mellitus (OVADIA), a study of ~5000 women with T1DM, also found an identical age at menopause in those with T1DM as compared with those without (49.8 versus 49.8) [28]. Finally, Kim et al reported that women with T1DM had similar age at menopause compared to the average age at menopause in the U.S. and also did not find an association between severity of diabetes or intensity of glucose control and age at menopause[29].

Type 2 Diabetes Mellitus (T2DM)

Menarche in Women with T2DM—Although women who experience early menarche have a higher risk of later diabetes,[30] we found no investigations on the timing of menarche among girls with T2DM. We assume this is because none exist to date as prevalence of T2DM in pre-adolescent girls is low. However, given the recent increased incidence of type 2 diabetes in children [31], studies of menarche in girls with T2DM will likely become available in the near future.

Reproductive Years in T2DM—Although the relationship between menstrual irregularity, ovarian morphology (especially large ovaries with large numbers of follicles), and diabetes is well established due to investigations of polycystic ovarian syndrome, few studies describe the menstrual cycle and ovarian characteristics of women with existing T2DM. Five studies regarding this topic were identified by our search strategy. Oligomenorrhea was assessed in two studies and defined differently between studies[32, 33]. Zargar et al described the prevalence of oligomenorrhea, defined as menstrual cycles no more frequently than every 35 days, as significantly higher among North Indian women with T2DM ($n=105$) as compared with healthy controls ($n=60$) (12% versus 0%; $p=0.014$)[32].

Peppard et al studied premenopausal women with T2DM (n=30) with 8 of 30 (27%) women reporting having fewer than eight menses annually[33].

Four studies have evaluated AFC and presence of polycystic ovarian morphology in women with T2DM. In one report of women with T2DM ranging in age from 24–41 years (n=38), 31 of 38 (82%) had polycystic ovaries on ultrasound[34]. The aforementioned Zargar study reported a much higher prevalence of polycystic ovaries among North Indian women with T2DM as compared with controls (61% versus 36.7%; $p<0.003$)[32]. Kelestimer et al also reported a “more common” prevalence of polycystic ovaries among women with T2DM (31/92, 34%) as compared with controls, although the exact prevalence among their controls was not provided[35].

In contrast, Isik et al[36] reported that women with T2DM had a lower, rather than higher AFC compared to controls. A major limitation of all of these studies is that they are cross-sectional. A longitudinal study of ovarian aging in women with T2DM seems needed. This would provide a better understanding of the trajectory of ovarian reserve in women with T2DM as well as changes in ovarian morphology. Such longitudinal examination might reconcile the conflicting results described above.

Menopause in T2DM

Timing of Menopause: Body mass index (BMI) is associated with age at menopause, with several studies showing that more overweight women experience later menopause[37]. Since overweight women are more likely to have T2DM, it is logical to conclude that women with T2DM may have later menopause. However, in crosssectional and longitudinal studies, women with T2DM appear to have earlier ages of menopause than women without diabetes.

In the longitudinal and multiethnic Study of Women’s Health Across the Nation (SWAN) Bone study (n=2171), women with diabetes near the beginning of the study experienced a significantly earlier age their final menstrual period (FMP) than women without diabetes (at age 49.1 versus 52.4; $p=0.002$)[38]. The study further noted that although all women in SWAN were premenopausal (54%) or early peri-menopausal (46%) at baseline, a significantly higher proportion of women with DM of any kind transitioned to early peri-menopause as compared to those without diabetes (58% vs. 45%, $p<0.001$)[38]. Sekhar et al also found a lower average age of menopause among those with T2DM as compared with those without (44.65 years versus 48.2 years; $p<0.01$). In addition, early menopause (before age 45) was also more common among women with T2DM as compared with women without (50% versus 17%; p-value not provided)[39]. These results are consistent with the findings of a study of women in Latin America that reported a more than two-fold higher prevalence of early menopause among 40–44-year-old women with T2DM (n=410) as compared with women without (n=5669) (29% versus 13.2%; OR 2.76: CI 1.32–5.34)[40].

In contrast, Lopez-Lopez et al found that Mexican women with T2DM (n=409) experienced a similar age at menopause as compared with women without diabetes (n=404) (49.8 versus 49.6; p not provided)[41].

Similarly, Brand et al [3] found no relationship between diabetes and age at menopause (HR 0.94; 95% CI 0.89–1.01). In fact, women with a later onset of diabetes (after age 50 and thus more likely to have T2DM) had a lower hazard of early menopause (HR = 0.81; 95% CI 0.70–0.95)[3]. As these studies were not designed to ascertain diabetes in population-based samples and also assessed age at menopause by self-report, the longitudinal relationship between diabetes and age at menopause is not clear. Ultimately, these findings, along with their discrepancies and shortcomings, support the need for further longitudinal study.

Conclusion

This review suggests that diabetes affects ovarian function throughout the reproductive lifespan. In women with T1DM versus T2DM, the process of reproductive aging appears similar in some ways and distinctive in others. Women with T1DM are more likely to have delayed menarche, menstrual dysfunction and possibly an earlier menopause. Their reproductive aging trajectories have improved over time, but dysfunction remains high despite improved treatment in recent decades. This dysfunction likely leads to decreased reproductive years. Studies of women with T2DM, a more heterogeneous group, do not consistently show statistically significant differences in reproductive aging as compared with healthy women, although there is a trend towards earlier menopause.

The impact of diabetes on reproductive function and aging is a complex phenomenon. A multitude of factors may disrupt hypothalamic, pituitary, and ovarian function. Microvascular damage, such as the damage that causes proliferative retinopathy and nephropathy, may extend to endocrine organs. Longitudinal studies evaluating potential mechanisms of ovarian aging in women with diabetes are needed given the increasing burden of diabetes among women at younger reproductive ages. This enhanced knowledge may provide tools to predict and prevent unwanted consequences in women throughout their reproductive lifespan.

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Highlights

- Reproductive aging is negatively affected by diabetes.
- The reproductive lifespan of women with type 1 diabetes is shorter than average because of later menarche and earlier menopause.
- Reproductive aging among women with type 2 diabetes is more variable; early menopause may occur more often.

Table 1

Sample size of girls/women with Type 1 Diabetes Mellitus (T1DM), country of origin, and age at menarche in selected studies of menarche in T1DM.

			Age at menarche	
			T1DM	Control
Kjaer, 1992	n=245	Denmark	13.6	13.4 ^{ns}
Dorman, 2001	n=143	US	13.5	12.6 ^{***}
Elamin, 2006	n=35	Sudan	15.1	13.3 [#]
Rohrer, 2007	n=579	Germany	13.2	12.7 ^{***}
Picardi, 2008	n=162	Italy	12.6	12.3 [*]
Hsu, 2010	n=41	Taiwan	13.0	12.1 [*]
Schweiger, 2010	n=290	US	13.2	n.a.
Raha, 2013	n=103	India	14.0	12.3 [#]
Zachurzok, 2013	n=47	Poland	13.1	12.0 [*]
Gomes, 2015	n=1527	Brazil	12.7	n.a.

*
<0.05,

**
<0.01,

<0.001

population estimate as comparator group

n.a. = not available

ns = not significantly different