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Review

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.

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1. 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.

2. 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").

2.1. 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.

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 et al. [7]	n = 245	Denmark	13.6	13.4^{ns}
Dorman et al. [9]	n = 143	US	13.5	12.6***
Elamin et al. [12]	n = 35	Sudan	15.1	13.3[a]
Rohrer et al. [13]	n-579	Germany	13.2	12.7***
Picardi et al. [14]	n = 162	Italy	12.6	12.3*
Hsu et al. [42]	n = 41	Taiwan	13.0	12.1*
Schweiger et al. [11]	n = 290	US	13.2	n.a.
Raha et al. [15]	n = 103	India	14.0	12.3[a]
Zachurzok et al. [16]	n = 47	Poland	13.1	12.0*
Gomes et al. [43]	n = 1527	Brazil	12.7	n.a.

*<0.05, **<0.01, ***<0.001.
[a] Population estimate as comparator group.
n.a. = not available.
ns = not significantly different.

3. Results/Discussion

3.1. Type 1 diabetes mellitus (T1DM)

3.1.1. 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].

3.1.2. Reproductive years in T1DM

3.1.2.1. 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