

EDITORIAL

Addressing fertility and reproductive issues in female adolescents with diabetes



Paulina M Merino^{1,2}



Joel E Riquelme¹



Ethel Codner^{*1}



“...the fear of hypoglycemia, unexpected death and severe chronic complications may be associated with the fear of dying without having experienced sex or maternity and may have a role in early sexual behavior...”

Fertility and pregnancy prevention are topics that are seldom considered in the routine care of adolescents with diabetes. The presence of unsafe sexual practices [1] and other risky behaviors in this young population [2] is striking because unprotected sex may pose higher risks to adolescents with Type 1 diabetes (T1D) than to the general population. The challenges of living with a chronic condition and the fear of hypoglycemia, unexpected death and severe chronic complications may be associated with the fear of dying without having experienced sex or maternity and may have a role in early sexual behavior during adolescence [3].

One of the explanations for the lack of pregnancy prevention in adolescents' with T1D is their misconception that they are infertile due to the presence of menstrual irregularities and poor metabolic control. Menstrual irregularities, particularly oligomenorrhea, are very prevalent in young

adolescents with T1D [4]. The prevalence of this abnormality increases with deteriorating metabolic control. It has recently been shown that the duration of the menstrual cycle is prolonged by 5.1 days for each 1% increase in glycated hemoglobin [5].

However, it is important to consider that the presence of menstrual disturbances is not necessarily a reflection of anovulation, as previously thought. In the 1950s, Bergqvist showed that adult women with T1D displayed signs of ovulation, such as variations in basal temperature, despite the presence of menstrual disturbances [6]. Recently, a prospective study evaluated ovulation in adolescents with and without T1D in 168 and 281 menstrual cycles, respectively [7]. This study showed that adolescents with T1D had similar rates of ovulation compared with healthy nondiabetic adolescents (34.5 and 36.3%, respectively), although both groups had a high prevalence of menstrual irregularities,

“...recommendations for women with diabetes suggest that women who do not have any microvascular complications and have had diabetes for less than 20 years ... are suitable for any type of reversible contraception.”

¹Institute of Maternal & Child Research, School of Medicine, University of Chile, Casilla 226-3 Santiago, Santiago, Chile

²Departments of Pediatrics, Campus Centro, School of Medicine, University of Chile

*Author for correspondence: Tel.: +56 2 977 0862; Fax: +56 2 424 7240; ecodner@med.uchile.cl

oligomenorrhea was present in 35 and 25% of the girls with and without T1D, respectively. Data showing the preservation of ovulatory function in young adolescents with T1D are in agreement with a previous epidemiologic study in young women with T1D showing a similar or even higher rate of pregnancy in young women with diabetes compared with the general population, particularly in those diagnosed during the last two decades [8].

Another frequent explanation that adolescents with T1D give for thinking that they cannot become pregnant is the presence of poor metabolic control. In the aforementioned study of ovulation in adolescents with T1D, an inverse relationship between HbA1c levels and ovulatory function was observed, but some of the girls with insufficient metabolic control had regular ovulatory cycles, as shown by the presence of monthly ovulatory cycles in some of the girls with HbA1c levels above 11% [7]. In addition, the assessment of ovulatory function in girls with optimal metabolic control, as shown by an HbA1c level lower than 7.5%, demonstrated that there was a tendency to observe an even better ovulatory rate in these patients than in healthy controls of a similar age. Therefore, ovulation in adolescents with T1D with different degrees of metabolic control is preserved, and the presence of poor metabolic control should not lead the girls to think that they cannot become pregnant.

Reproductive function in adolescents with Type 2 diabetes (T2D) has not been as well studied as in T1D, despite the increasing prevalence of this form of diabetes in the young population. Adolescents with T2D are insulin resistant and obese, and the disease is frequently associated with polycystic ovary syndrome, which could affect the future fertility of this group of patients [9]. Poor metabolic control in adolescents with T2D is even more prevalent than in T1D teenagers, making it important to educate these patients about the risks of becoming pregnant in the face of hyperglycemia [10]. However, T2D adolescents are less likely to receive preconception counseling than patients with T1D [11].

The current recommendations focus on the early education of girls with diabetes. The American Diabetes Association suggests that “starting at puberty, preconception counseling should be incorporated in the routine diabetes clinic visit for all women of childbearing

potential” [12]. According to the International Society of Pediatric Diabetes, preconception counseling in patients with diabetes should include education about the risk of fetal malformations if they become pregnant without good metabolic control and the importance of good glycemic control before and throughout pregnancy [13]. Despite the presence of these recommendations, adolescents with T1D are less likely to receive contraceptive counseling and sexual education than healthy girls, resulting in a lack of awareness of the need to safely and consistently use birth control [14–16]. This behavior may be explained by ambivalent attitudes by medical teams and parents, mainly mothers [17].

Once a girl with diabetes becomes sexually active, she should already be educated about how to avoid an unplanned pregnancy [1]. Preconception counseling includes a continuum of educational activities. These involve a first stage intended to develop ‘awareness’, a second stage named ‘overview’, which includes women contemplating pregnancy and a third stage called ‘in-depth’, for women actively planning pregnancy who require intensive metabolic control. Pediatricians caring for adolescents with diabetes should focus repeatedly on the awareness stage [16].

The choice of adequate contraception should consider medical issues and individual religious and cultural preferences [13,18]. Recently, WHO released medical eligibility criteria to help health professionals in the election of contraceptives for different groups of women, including those with diabetes [19]. The recommendations for women with diabetes suggest that women who do not have any microvascular complications and have had diabetes for less than 20 years, as is the case for the majority of adolescents with diabetes, are suitable for any type of reversible contraception. However, women with micro- or macro-vascular disease or diabetes duration greater than 20 years should avoid combined estrogen/progestin contraception and favor an intrauterine device, or progestin-only and barrier methods. For adolescents with diabetes, similar to their nondiabetic counterparts, a dual method is advised, including a hormonal method and condoms to prevent sexually transmitted infections, which are highly prevalent in this age group [4].

Part of the reluctance to use hormonal contraception in adolescents arises from concerns

“Ovulation in adolescents with Type 1 diabetes with different degrees of metabolic control is preserved ... the presence of poor metabolic control should not lead the girls to think that they cannot become pregnant.”

about the effects of these medications on glucose metabolism, diabetes-related complications and weight gain. Unfortunately, few studies have evaluated these factors, and all of the performed studies have evaluated the metabolic impact of these medications in adult women with diabetes. A recent Cochrane review assessed the literature available regarding hormonal and nonhormonal contraceptives in women with T1D and T2D and found only three randomized controlled trials. This systematic review demonstrated that no studies have determined whether progestin-only and combined contraceptives differ from nonhormonal contraceptives in regards to diabetes control, lipid metabolism and complications [20]. Therefore, similar to what is stated by WHO, low-dose combined oral contraceptives may be considered a safe and effective option for younger women with uncomplicated well-controlled diabetes [21].

There is a wide array of available hormonal contraception, including different types of progestins, ranging from first- to fourth-generation drugs, and the presence of different routes of administration, including oral, transdermal, vaginal and injectable. However, there are no data to indicate the best choice for adolescents with diabetes. At this time, there is no basis for the denial of any of the aforementioned choices of hormonal contraception for adolescents with diabetes. It is our opinion that progestin-only pills should be seldom recommended for young women because of an unacceptable failure rate

when administered orally. There are also concerns about reduced bone mineral density in adolescents using depot medroxyprogesterone acetate and contraceptives with less than 30 µg of ethinyl-estradiol. Therefore, we do not recommend these for young patients with T1D who are prone to osteopenia [1,22]. This side effect has not been shown for the levonorgestrel implant.

Clearly, at this young age, diabetes does not impair fertility. Notwithstanding, adolescents with diabetes typically do not receive the education necessary to understand this fact. Therefore, physicians should include education on the presence of ovulation, regardless of menstrual irregularities and insufficient metabolic control, in routine diabetes care. Through an increased awareness on reproductive issues in patients with diabetes, we look forward to the appearance of sexual education programs and future studies that will determine the best hormonal contraception choice for these young women.

Financial & competing interests disclosure

This manuscript has been partially supported by Fondecyt Grants 1100123 and 1050452 to E Codner. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

“Through an increased awareness on reproductive issues in patients with diabetes, we look forward to the appearance of sexual education programs and future studies that will determine the best hormonal contraception choice for these young women.”

References

- Codner E, Soto N, Merino PM. Contraception, and pregnancy in adolescents with Type 1 diabetes: a review. *Pediatr. Diabetes* 13(1), 108–123 (2012).
- Martinez-Aguayo A, Arana JC, Fernandez D, Gleisner A, Perez V, Codner E. Tobacco, alcohol, and illicit drug use in adolescents with diabetes mellitus. *Pediatr. Diabetes* 8(5), 265–271 (2007).
- Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: challenges living, challenges treating. *Lancet* 369(9571), 1481–1489 (2007).
- Codner E, Merino PM, Tena-Sempere M. Female reproduction and Type 1 diabetes: from mechanisms to clinical findings. *Hum. Reprod. Update* 18(5), 568–585 (2012).
- Gaete X, Vivanco M, Eyzaguirre FC *et al*. Menstrual cycle irregularities and their relationship with HbA1c and insulin dose in adolescents with Type 1 diabetes mellitus. *Fertil. Steril.* 94(5), 1822–1826 (2010).
- Bergqvist N. The gonadal function in female diabetics. *Acta Endocrinol.* 15, S3–S20 (1954).
- Codner E, Eyzaguirre FC, Iniguez G *et al*. Ovulation rate in adolescents with Type 1 diabetes mellitus. *Fertil. Steril.* 95(1), 197–202 (2011).
- Jonasson JM, Brismar K, Sparen P *et al*. Fertility in women with Type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care* 30(9), 2271–2276 (2007).
- Whitworth KW, Baird DD, Stene LC, Skjaerven R, Longnecker MP. Fecundability among women with Type 1 and Type 2 diabetes in the Norwegian Mother and Child Cohort Study. *Diabetologia* 54(3), 516–522 (2011).
- Lapolla A, Dalfrà MG, Di Cianni G, Bonomo M, Parretti E, Mello G. A multicenter Italian study on pregnancy outcome in women with diabetes. *Nutr. Metab. Cardiovasc. Dis.* 18(4), 291–297 (2008).
- Slocum JM. Preconception counseling and Type 2 diabetes. *Diabetes Spectrum* 20(2), 117–123 (2007).
- American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care* 35(Suppl. 1), S11–S63 (2012).
- Court JM, Cameron FJ, Berg-Kelly K, Swift PG. Diabetes in adolescence. *Pediatr. Diabetes* 10(Suppl. 12), S185–S194 (2009).
- Lawrenson RA, Leydon GM, Williams TJ, Newson RB, Feher MD. Patterns of contraception in UK women with Type 1 diabetes mellitus: a GP database study. *Diabet. Med.* 16(5), 395–399 (1999).

- 15 Manolopoulos K, Kiess W, Braems GA *et al.* Which contraceptive methods are recommended for young women with Type 1 diabetes mellitus? A survey among gynaecologists in Greece. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 99(2), 232–237 (2001).
- 16 Charron-Prochownik D, Sereika SM, Wang SL *et al.* Reproductive health and preconception counseling awareness in adolescents with diabetes: what they don't know can hurt them. *Diabetes Educ.* 32(2), 235–242 (2006).
- 17 Hannan M, Happ MB, Charron-Prochownik D. Mothers' perspectives about reproductive health discussions with adolescent daughters with diabetes. *Diabetes Educ.* 35(2), 265–273 (2009).
- 18 American Academy of Pediatrics: Committee on Psychosocial Aspects of Child and Family Health and Committee on Adolescence. Sexuality education for children and adolescents. *Pediatrics* 108(2), 498–502 (2001).
- 19 WHO. *Medical Eligibility Criteria for Contraceptive Use (4th Edition)*. WHO Press, Geneva, Switzerland (2009).
- 20 Visser J, Snel M, Van Vliet HA. Hormonal versus non-hormonal contraceptives in women with diabetes mellitus Type 1 and 2. *Cochrane Database Syst. Rev.* (4), CD003990 (2006).
- 21 Schwarz EB, Maselli J, Gonzales R. Contraceptive counseling of diabetic women of reproductive age. *Obstet. Gynecol.* 107(5), 1070–1074 (2006).
- 22 Agostino H, Di Meglio G. Low-dose oral contraceptives in adolescents: how low can you go? *J. Pediatr. Adolesc. Gynecol.* 23(4), 195–201 (2010).