Pediatric Diabetes

ISPAD International Society for Pediatric and Adolescent Diabetes

Pediatric Diabetes 2012: 13: 108–123
doi: 10.1111/j.1399-5448.2011.00825.x

Pediatric Diabetes

Review Article

Contraception and pregnancy in adolescents with type 1 diabetes: a review

Codner E, Soto N, Merino PM. Contraception and pregnancy in adolescents with type 1 diabetes: a review.
Pediatric Diabetes 2012: 13: 108–123.

Adolescence is a critical period for girls with type 1 diabetes mellitus (T1D). Reproductive issues, such as menstrual abnormalities, risk of an unplanned pregnancy, and contraception, should be addressed during this phase of life. This paper reviews several reproductive issues that are important in the care of adolescents, including pubertal development, menstrual abnormalities, ovulatory function, reproductive problems, the effects of hyperglycemia, contraception, and treatment of an unplanned pregnancy.

A review of the literature was conducted. A MEDLINE search January 1966 to March 2011 was performed using the following MESH terms: puberty, menarche, ovary, polycystic ovary syndrome, menstruation, contraception, contraception-barrier, contraceptives-oral-hormonal, sex education, family planning services, and pregnancy in adolescence. This literature search was cross-referenced with an additional search on diabetes mellitus-type 1, diabetes complications, and pregnancy in diabetes. All published studies were searched regardless of the language of origin. Bibliographies were reviewed to extract additional relevant sources.

Ethel Codner[a], Néstor Soto[b] and Paulina M. Merino[a,c]

[a]Institute of Maternal and Child Research (I.D.I.M.I.), School of Medicine, University of Chile, Santiago, Chile; [b]Endocrinology Unit, Hospital San Borja-Arriarán, Santiago, Chile; and [c]Department of Pediatrics, School of Medicine, University of Chile, Santiago, Chile

Key words: adolescence – complications – contraception – diabetes mellitus – menarche – menstrual cycle – menstruation – ovulation – pregnancy – puberty – type 1 diabetes mellitus

Corresponding author:
Ethel Codner, MD,
Institute of Maternal and Child Research (I.D.I.M.I.),
School of Medicine,
University of Chile,
Casilla 226-3,
Santiago, Chile.
Tel: (562) 977-0862;
fax: (562) 424-7240;
e-mail: ecodner@med.uchile.cl

Submitted 26 May 2011. Accepted for publication 1 September 2011

Puberty and ovarian function

Pubertal development

The timing of puberty and menarche and the age of childbearing have changed during recent decades in the general population. A trend toward earlier menarche, also known as the secular trend, has been observed since the end of the 19th century in healthy adolescents (1, 2). An earlier age of the onset of puberty as assessed by the presence of thelarche has also been described in healthy girls (3–5). Several decades ago, girls with T1D frequently exhibited severe pubertal delay associated with poor metabolic control (6, 7), although this is rarely seen now.

Two recent studies evaluated the age of the onset of puberty in girls with T1D. A Chilean group evaluated a large group of girls with T1D ($N = 110$) and a concomitant control group ($N = 576$) that were carefully matched by ethnicity and socio-economic status (8). A similar age of onset of thelarche in both groups was observed, occurring one and a half years earlier than historical controls. The authors concluded that both groups followed the secular trend toward earlier onset of puberty which has also been described in the USA in the general population (1).

Rohrer et al. performed a large longitudinal study of 2578 girls from 200 German centers that were participating in a quality control study for diabetes

patients (9). The researchers showed that thelarche was observed six months later in girls with T1D than in the controls, although the reported age was within the normal range for both groups. The authors reported that a higher body mass index (BMI) and a lower HbA1c were associated with earlier onset of puberty.

Very few studies have focused on the final stages of breast and pubic hair development in girls with T1D. The two studies previously mentioned showed a delay of between two and six months to reach the final stages of breast development and pubic hair growth (8–10).

Most studies have observed that the age of onset of puberty in girls with T1D is within the normal range and follows the secular trend for earlier development observed in the general population. Although a mild delay of pubertal onset and the final stages of pubertal development may be observed in some patients with T1D, due in part to poor metabolic control, celiac, and thyroid disease should be ruled out as possible causes of delayed development.

Age of menarche and the secular trend

The secular trend of the age of menarche observed in girls with T1D and the general population is shown in Fig. 1. The age of menarche in girls with T1D has followed the secular trend observed in healthy girls. Although a delay has been noted in girls with T1D, the magnitude of this delay has decreased throughout the last several decades. This decrease has been especially noticeable in the USA. In the 1940s and 1950s, menarche occurred 2 years later in girls with T1D compared to the general population, and a significant proportion of the T1D patients exhibited primary amenorrhea into their late teens (reviewed by Bergqvist (6)). Recent case control studies (Fig. 1) have shown a mild delay in the age of menarche in girls with T1D, ranging from 2 to 9 months in countries in Europe and North and South America (8, 9, 11–16).

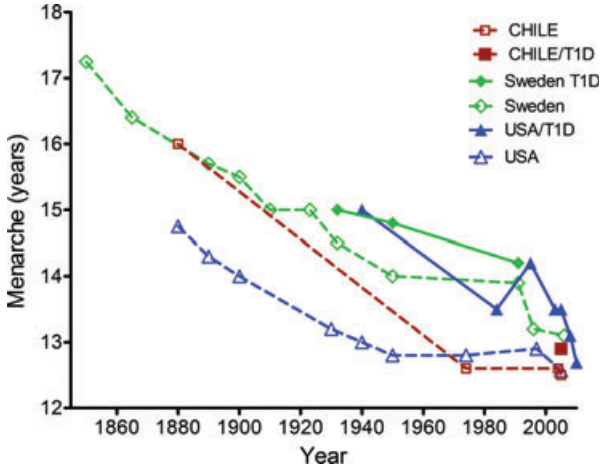

Fig. 1. The secular trend of menarche. The secular trend of the age of menarche is shown for the general population since the 19th century (2, 5, 153) and for girls with type 1 diabetes (T1D) since the 1940 decade (6, 8, 10, 11, 14, 154).

Delayed menarche has only been observed in patients with prepubertal or premenarcheal onset of T1D (13, 14, 16–18). Additional factors associated with a delay in the age of menarche are poor metabolic control (9, 11), lower BMI (8, 9, 11) and a longer duration of T1D (9, 11). Danielson et al. (11) observed a delay of 1.3 months in the age of menarche for each percentage point increase in glycated hemoglobin. This delay was later confirmed in other studies (9, 16). However, Picardi et al. observed a mild delay of menarche in girls with an HbA1c value lower than 7.5% (12), indicating that several other factors may be involved in the delay of menarche in girls with T1D. For example, lower insulin doses may be associated with delayed menarche, possibly because of the effects of insulin on the central nervous system (9).

The clinical significance of the delay in the age of menarche depends on the magnitude of the postponement. Late menarche is associated with irregular menses in girls with T1D (17, 18) and decreased bone mass in healthy girls (19). Theoretically, the association of late menarche and menstrual irregularities with estrogen deficiency could play a role in the cardiovascular complications observed in women with T1D (20).

Menstrual irregularities

Having regular menstrual cycles associated with ovulation is the final step toward maturity in reproductive development. Several retrospective studies have shown an increased prevalence of menstrual cycle abnormalities in adult women with T1D (13, 17, 18, 21), but only a few studies have evaluated these irregularities in adolescents with T1D (15, 22–25).

Because menstrual periods are longer during adolescence, the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) have published specific criteria for this age group (26, 27). Physiologically, the average menstrual cycle length during adolescence is approximately 32–34 days, and a normal menstrual cycle interval has been defined as between 21 and 45 days in the first 5 years following menarche (27, 28). Several studies that evaluated menstrual dysfunction during adolescence in girls with T1D used the 35 day criteria for the diagnosis of oligomenorrhea, which is close to physiologic duration of the menstrual cycle, and may report an exceedingly high prevalence of menstrual dysfunction as a result (15, 22, 23, 25). Gaete et al. recently used the adolescent criteria of menstrual irregularities to prospectively study 56 adolescents with T1D treated with greater than or equal to three daily doses of insulin

Table 1. Characteristics of menstrual cycles according to metabolic control in girls with type 1 diabetes (T1D) compared with the control group

	Control	T1D	HbA1c < 7.6%	T1D HbA1c = 7.6–8.9%	HbA1c > 9%
n	56	56	15	18	22
Menarche (years)	12.1 ± 1.0	12.6 ± 1.3*	12.2 ± 0.9	12.5 ± 1.4	13.0 ± 1.3**
Menstrual cycle duration (days)	32.7 ± 8.6	48.0 ± 38.9	34.9 ± 8.9	48.6 ± 34*	57 ± 52.3***
CV (%)	24.3 ± 18.7	23.7 ± 18.4*	27.6 ± 15.6	35.5 ± 17.8*	27.4 ± 21.7
At least one cycle with (%):					
Oligomenorrhea	19.6***	58.9	53.3*	72.2***	54.5**
Amenorrhea	1.7†	10.7	0	11.1	18.2*
Polymenorrhea	44.6	39.3	60.0	50.0	18.2*

Reprinted with permission from Ref. (24)
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, †$p = 0.05$.

and 56 healthy adolescent girls (24). This study demonstrated that girls with T1D had longer menstrual cycles and greater cycle variability compared to the control group (Table 1). Girls with T1D showed a mean cycle duration of 48 days, which was significantly longer than the 32-day cycle duration observed in the control group and the 32- to 34-day cycle duration observed in previous reports of healthy adolescents (27, 29, 30). Sixty percent of the patients with T1D experienced at least one episode of oligomenorrhea during the 6-month observation period, which was significantly higher than the 20% observed in control girls (odds ratio (OR) = 5.9). Eighty-one percent of the girls with T1D and 59% of the controls had at least once cycle with an abnormal duration (OR = 5.9). The prevalence of polymenorrhea was similar in both groups. Menstrual irregularities are a frequent problem in adolescents with T1D, and the prevalence of such irregularities in this group is even higher than that previously reported in adults with T1D (13, 17, 18, 31, 32).

Metabolic control is the most important determinant of menstrual irregularities in adolescents with T1D (22–25). Gaete et al. showed that HbA1c was the only risk factor identified in determining menstrual cycle length in T1D; regression analysis showed that menstrual cycle duration is prolonged by 5.1 days for each point increase in HbA1c (25). The study by Gaete et al. showed that some abnormalities in the menstrual cycle were observed in girls with optimal metabolic control (HbA1c lower than 7.6%) who exhibited twice the prevalence of oligomenorrhea than the controls (OR = 4.7). Menstrual abnormalities were prevalent in girls with T1D and intermediate metabolic control (HbA1c = 7.6–8.9%), who displayed longer and more irregular cycles, with 70% reporting at least one cycle longer than 45 days.

An increased variability in the menstrual cycle in teens with T1D has been shown (25) even when data were adjusted for HbA1c levels and gynecological age, which was associated with higher insulin doses. It has been postulated that higher insulin doses may affect ovarian steroidogenesis or folliculogenesis and lead to irregular cycles (33, 34).

Despite treatment with multiple daily insulin doses, menstrual irregularities are a prevalent problem during adolescence for individuals with T1D. Longer menstrual cycles and higher variability in menstrual lengths are frequently observed in these patients. Although these symptoms become less severe after adolescence, menstrual irregularities should be included in the list of critical problems during adolescence for girls with T1D.

Ovulation

Very few studies have evaluated ovulatory function in women with T1D. In healthy women, the presence of regular menses is associated with ovulatory cycles (35, 36). Oligomenorrhea suggests ovulatory dysfunction but may be a result of ovulatory cycles with longer follicular phases (35). Therefore, the presence of menstrual abnormalities is not necessarily a good indicator of ovulatory function.

Codner et al. recently followed a group of nonhyperandrogenic adolescents with T1D (n = 31) and a group of healthy girls (n = 52) (37). The participants were recruited if less than 6 months had elapsed as menarche or if they were close to reaching the second or third year postmenarche. Each girl was followed for an average of five cycles, and ovulation was assessed through the measurement of salivary progesterone on days 13, 18, 23, and 28 of each cycle. A total of 168 and 281 menstrual cycles were studied in girls with T1D and controls, respectively. The authors observed that ovulation was not decreased in girls with T1D. The proportion of ovulatory cycles and the number of ovulations every 100 days was similar in the T1D and control groups (34.5 and 36.3%, respectively; Fig. 2A and B). The proportion of girls that did not have any ovulatory cycles was similar in both groups (19.4 and 19.2% in the T1D and control groups, respectively), although 35% of the girls with T1D had at least one cycle of oligomenorrhea. Regression analyses showed that the presence of T1D

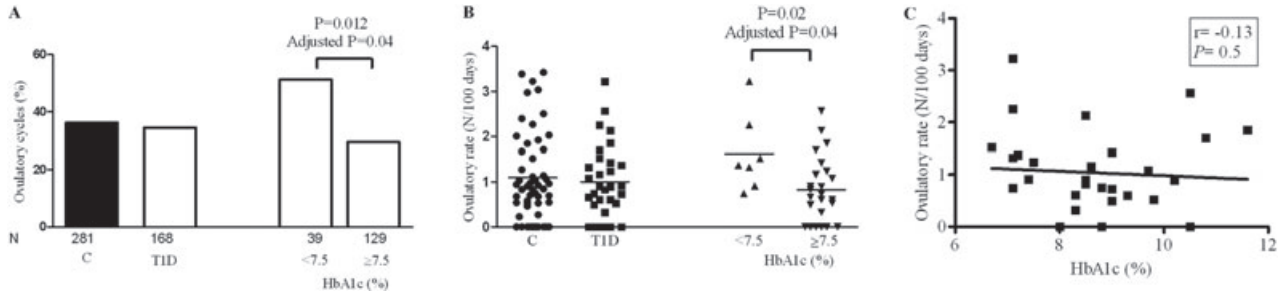

Fig. 2. Ovulation in adolescents with type 1 diabetes (T1D) and controls and the relationship between ovulation and optimal metabolic control in adolescents with T1D. (A) Proportion of the total cycles that are ovulatory. Unadjusted analysis was performed with Pearson's chi-squared test. The number of cycles studied in each group is shown below each bar. p = 0.012, adjusted p = 0.04. (B) Ovulatory rate. p = 0.02, adjusted p = 0.04. (C) Correlation of ovulatory rate with hemoglobin A1c (HbA1c) levels (r = −0.13, p = 0.5). [Reprinted with permission from Ref. (37).]

did not significantly affect ovulatory function. These data are in accordance with studies evaluating the etiology of infertility, which have shown that T1D is a rare cause of consultation in infertility clinics (38–40).

Metabolic control had a slight effect on the rate of ovulation. As shown in Fig. 2A and B, a higher percentage of ovulatory cycles and an increased rate of ovulation every 100 days were observed in girls with T1D with optimal metabolic control compared to girls with insufficient metabolic control. However, when HbA1c was considered as a continuous variable (Fig. 2C), no correlations with the rate of ovulation were observed, which was reflected by the fact that some girls with high HbA1c levels still had a considerable number of ovulatory cycles.

In conclusion, ovulation is present in girls with T1D during adolescence regardless of their metabolic control and the presence of menstrual irregularities. These findings highlight the importance of pregnancy prevention in all adolescents with T1D and are in accordance with studies performed over 50 years ago by Bergqvist, who showed that adult women with T1D demonstrated signs of ovulation, such as variations in basal temperature, despite menstrual irregularities. In 1984, Steel showed a delay in the day of ovulation in 11 adult women with T1D who were trying to get pregnant, suggesting a longer follicular phase, which may explain the presence of ovulation despite longer menstrual cycles (41).

Pathophysiology of reproductive problems in women and adolescents with T1D

Manifestations of T1D in the reproductive system may be explained by abnormal insulin levels. The importance of insulin action on reproductive function is highlighted by the fact that insulin receptors are expressed in most tissues of the body, including organs not classically related to insulin metabolism, such as the hypothalamus, pituitary, ovaries, and uterus. Several

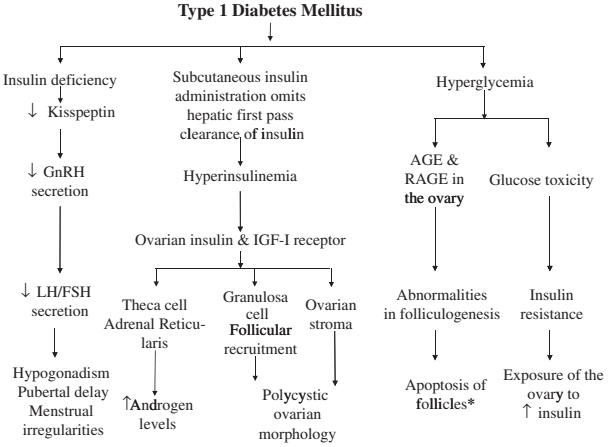

Fig. 3. Pathophysiology of abnormalities of ovarian function in type 1 diabetes mellitus. [Modified from Ref. (10).] *Apoptosis of follicles secondary to hyperglycemia has been demonstrated in animals. GnRh, Gonadotropin Releasing Hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; IGF-I, insulin-like growth factor-1; AGE, advanced glycation end-products; RAGE, receptor of advanced glycation end-products.

decades ago, reproductive abnormalities accompanying T1D resulted in hypogonadism because of insulin deficiencies. More recently, intensive treatment of T1D which frequently is associated with excessive insulin replacement has resulted in a decrease in the prevalence of hypogonadism but has led to the appearance of reproductive abnormalities due to insulin excess (Fig. 3).

Hypogonadotropic hypogonadism. The clinical manifestations of decreased gonadotropin secretion are the result of decreased insulin action in the central nervous system. Hypogonadotropic hypogonadism is present in women with uncontrolled T1D (42, 43) (Fig. 3, left panel). Similarly, studies in mice with streptozotocin-induced diabetes showed that the animals developed a hypogonadal state with

decreased luteinizing hormone/follicle stimulating hormone (LH/FSH) and estradiol levels, which was at least partially reversed after administration of insulin (44).

These findings were confirmed in knockout mice that lacked brain insulin receptors and developed hypogonadotropic hypogonadism (45). Knockout mice without brain insulin receptors responded to exogenous GnRH by increasing LH levels. These data suggest that the central nervous system decreases GnRH stimuli during periods of insulin deficiency (45). Recently, Castellano et al. demonstrated that hypogonadism in insulin-deficient mice with streptozocin-induced diabetes was a result of decreased kisspeptin expression in the hypothalamus. The authors also showed that administration of kisspeptin, a peptide that stimulates GnRH secretion and has a role in regulating the onset of puberty, restored gonadotropin and steroid levels in the mice (46, 47). The pathophysiological cascade of hypogonadism secondary to decreased kisspeptin levels observed in insulinopenic diabetes has also been described in unfed animals, suggesting that hypogonadism because of a diminished kisspeptin levels is a common event as a result of several conditions that involve underfeeding (48).

Hyperandrogenism and polycystic ovaries. Clinical manifestations of hyperandrogenism have been demonstrated in adult women (31, 49) with T1D (Fig. 3, middle panel), but biochemical findings suggesting milder forms of this complication have been shown during childhood and adolescence (50). Recently, Codner et al. studied a group of prepubertal girls (3–9 years old) who had higher dehydroepiandrosterone-sulfate (DHEA-S) and androstenedione levels than controls during childhood (50), which suggests exaggerated androgen secretion during this period, as has been previously reported in boys (51). The same hormonal profile during childhood was observed in other groups of girls at risk of developing polycystic ovarian syndrome later in life and may be a result of the presence of the insulin receptor in the adrenal reticularis (52, 53).

There is scarce information about the prevalence and severity of hyperandrogenism during adolescence. A higher hirsutism score was observed in a group of pubertal girls with T1D, up to 2 years postmenarche, than in the controls (54). Biochemical evaluation suggested the presence of functional ovarian hyperandrogenism at Tanner Stage 5, as shown by higher levels of 17OH progesterone in the leuprolide test, in girls with T1D compared to the control group (54). Meyer et al. observed elevated total and free testosterone in pubertal girls with T1D in Tanner stage 5 (55). Girls with T1D and oligomenorrhea exhibited elevated stimulated 17OH progesterone in the leuprolide test (56).

Clinical and biochemical hyperandrogenism is prevalent in adult women with T1D. In 2000, Escobar-Morreale et al. showed that mild hirsutism and biochemical hyperandrogenism were present in 30 and 20% of the patients, respectively (32, 57). These findings were later confirmed (31). These studies have shown that clinical and biochemical hyperandrogism is milder in women with T1D and polycystic ovarian syndrome (PCOS) than in women with PCOS without diabetes (49, 57, 58). Risk factors for the development of hyperandrogenism in adult women include premenarcheal onset of T1D and the use of multiple insulin doses.

The use of exogenous insulin to treat T1D may contribute to the development of PCOS. Insulin is administered in a nonphysiological fashion via subcutaneous injection and is absorbed into the systemic circulation (59). This method of administration bypasses the hepatic first pass clearance and exposes the peripheral tissues to insulin levels that are higher than physiologically normal levels. Insulin receptors are present in all compartments of the ovary, including theca, granulosa, and stromal cells (34, 60), but insulin may also bind to insulin-like growth factor-1 (IGF-1) receptors in the ovary.

The theca cells of the ovary have a central role in secreting androgens, testosterone, and androstenedione. *In vitro* studies of theca cells obtained from healthy women have shown that insulin stimulates steroid secretion via the theca cells and increases the activity of several steroidogenic enzymes (34, 60). This response is greatly enhanced when the cells are simultaneously exposed to LH and insulin, which indicates that insulin may act as a co-gonadotropin (60).

Granulosa cells of the ovary have an important role in estrogen secretion and the maturation process of the follicle, leading to ovulation and a functional corpus luteum. In addition, granulosa cells secrete anti-Müllerian hormone (AMH), which is a marker of the number of small growing follicles known as the early-growing follicle pool. Insulin receptors are also expressed in granulosa cells, where they play a role in potentiating FSH-stimulated steroid secretion. This role is demonstrated by increased estrogen secretion in granulosa cells exposed simultaneously to insulin and FSH (33) and by stimulating the recruitment and growth of follicles (34, 61).

The effect of exogenous insulin treatment on the granulosa cell compartment of the ovary has been evaluated through the measurement of follicle numbers, ovarian volume, AMH and estradiol levels. In adult patients with T1D, increased ovarian volume and follicle numbers have been observed, resulting in polycystic ovaries in half of the patients (31).

AMH levels are correlated with the number of small follicles and are used as an index of ovarian reserve.

AMH levels are elevated in prepubertal girls with T1D, suggesting that insulin stimulates the growth of small follicles (50), which has also been observed in other groups of young girls who are at risk of developing PCOS (62).

The effects of exogenous insulin treatment on granulosa cells change once puberty begins and gonadotropin secretion increases. As previously mentioned, before puberty-elevated AMH levels are observed in girls with T1D, but after pubertal onset, their AMH levels are similar those found in healthy adolescents. Similarly, in adult women with PCOS and T1D, the levels of AMH were similar to the control group, which suggests that insulin may act as a co-gonadotropin by enhancing the maturation of large follicles (58). These results are different from results observed in other forms of PCOS [reviewed in Ref. (50)].

Hyperglycemia and ovarian reserve. Hyperglycemia may affect reproductive function by two mechanisms (Fig. 3, right panel). The first mechanism corresponds to insulin resistance secondary to glucose toxicity (63), a pathophysiologic event that affects ovarian function (64). The second mechanism by which hyperglycemia may negatively affect ovarian function is by directly affecting the ovary through the presence of advanced glycation receptors and products (65).

Hyperglycemia may play a role in the early decline of ovarian reserves and earlier onset of menopause in adult women with T1D (66, 67). Animal studies have suggested that hyperglycemia is involved in the abnormalities of folliculogenesis described in women with T1D. Several studies have investigated the effects of hyperglycemia on ovarian tissue from rats with diabetes induced by streptozotocin and found increased apoptosis of the oocyte and abnormal communication between somatic cells and gametes (68). Colton et al. showed that hyperglycemia may also affect folliculogenesis in diabetic rats (69).

In summary, several factors may be involved in altering ovarian function in girls with T1D. Insulin deficiency may lead to lower gonadotropin levels because of decreased GnRH secretion. In addition, hyperglycemia may affect the ovary both directly and through the induction of insulin resistance caused by glucose toxicity. Finally, higher insulin serum levels may lead to overstimulation of the insulin and IGF-1 receptors in the ovary, thus increasing steroid secretion and fostering the development of PCOS.

Contraception in adolescents with T1D

Routine care of the adolescent with T1D should include education about the risks of an unplanned pregnancy. The International Society of Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) recommend that education regarding pregnancy prevention and planning should begin before menarche (70, 71). Despite these recommendations, several studies have shown that adolescents with T1D are not aware of the risks of unplanned pregnancy and do not properly prevent this condition while engaging in risky behavior, especially during the late teen years (72, 73).

Charron-Prochownik et al. studied 80 girls with T1D and 37 matched controls and observed that teens with T1D had a significantly increased perception of the negative outcomes of sexual activity (e.g., unplanned pregnancy or pregnancy-related complications) but believed that they were not personally at risk. An unexpectedly low use of contraceptive methods, similar to the control group, was observed in adolescents with T1D (72). Another publication showed that more than half of the patients 'never thought' about diabetes and birth control, and only 6% mentioned the importance of regularly using birth control for women with diabetes (74). These data highlight the importance of the recommendation published by the American Academy of Pediatrics that '*Every pediatrician should integrate sexuality education into clinical practice with children from early childhood through adolescence. This education should respect the family's individual and cultural values*' (75).

The lack of education to prevent pregnancy in adolescents with T1D may be explained by ambivalent attitudes of the medical team toward recommending contraceptives to adolescents with diabetes, inadequate training in sexual counseling, and uncertainty about the appropriate age to provide this type of information (76). However, two recent studies showed that a preconception counseling program that includes an educative session and delivery of a book and CD were feasible and increased awareness about reproductive health issues in adolescents with T1D (77, 78).

Contraceptive alternatives for adolescents with T1D

Studies suggest that a combination of education and contraception promotion reduces the risk of unintended pregnancies in healthy girls. A Cochrane Database study recently reviewed more than 41 trials that included 95 662 teens and concluded that the combination of education and contraception promotion was highly successful in pregnancy prevention (71, 79). These results are likely applicable to girls with T1D.

The choice of a contraceptive method for women with T1D depends on the preferences and competencies of the patient, religious choices, duration of diabetes, the presence of complications, associated diseases, and risky behaviors, and even public politics (80, 81). The World Health Organization (WHO) states that age

Table 2. World Health Organization (WHO) eligibility criteria of contraceptives in women with type 1 diabetes

	Combined contraceptives				Progestin only			Intrauterine devices		Barrier
	Oral	Injectable	Patch	Vaginal ring	Oral	Deposit	Implant	Copper	Levonorgestrel	Condom
No micro or macrovascular disease	2	2	2	2	2	2	2	1	2	1
Diabetes of >20 years duration	3/4	3/4	3/4	3/4	2	2	2	1	2	1
Nephropathy/retinopathy/ neuropathy	3/4	3/4	3/4	3/4	2	3	2	1	2	1
Macrovascular disease	3/4	3/4	3/4	3/4	2	2	2	1	2	1

Adapted from Ref. (82).
1: Method may be used in any circumstances. 2: Method may be recommended. 3: Method is not usually recommended unless there are no appropriate, available or acceptable alternatives. 4: Method should not be used.

should not act as a barrier to reversible contraceptive methods for young adolescents (82). A careful history to exclude contraindications is sufficient to ensure safe provision, and the potential risks of certain contraceptive methods in younger adolescents must be balanced against the advantages of avoiding pregnancy.

In 2009, the WHO published new medical eligibility criteria for contraceptive use (82). In general, adolescents with diabetes duration of less than 20 years without vascular complications are eligible to use any method of contraception (Table 2).

Contraceptives are grouped as natural, barrier, hormonal, and intrauterine devices (IUDs). The different contraceptive choices available for adolescents and their reported efficacies are shown in Table 3. The best pregnancy prevention is achieved with hormonal methods and intrauterine devices, but they do not offer protection against sexually transmitted infections. The most popular choice of contraception in adolescents is the condom, with up to 60% of the girls reporting use of this method (83, 84). Condoms protect against pregnancy and infections and are readily

Table 3. Contraceptive alternatives available for adolescents

Method	Pearl index for perfect use (%)	Pearl index for typical use (%)	Adherence at 1 year of use (%)
No method	85	85	
Natural methods		20.5–25.0	51
• Calendar	5.0		
• Ovulation method	3.0		
Barrier methods			
• Male condom	2.0	15.0	53
• Female condom	5.0	21.0	49
• Diaphragm (with spermicides)	6.0	16.0	57
• Sponge (nulliparous)	9.0	16.0	57
• Cervical caps (nulliparous)	9.0	20.0	56
• Spermicides	18.0	29.0	42
• Coitus interruptus	4.0	19	No data
Hormonal methods			
• Combination pill	0.1	3.0	68
• Progestin only pill	0.5	8.0	68
• Combined patch	0.3	8.0	68
• Vaginal ring	0.3	8.0	68
• Combined monthly injectable	0.05	3.0	56
• Depot medroxyprogesterone acetate	0.3	3.0	56
• Etonogestrel-releasing contraceptive implant	0.05	0.05	84
Intrauterine devices (IUD)			
• Copper T-T380A	0.6	0.2	78
• Levonorgestrel IUD	0.2	0.2	80

Adapted from Ref. (74).
Efficacy is shown as the Pearl Index, which is defined as the number of pregnancies observed in 100 women during one year of exposure or the proportion of women experiencing an unintended pregnancy within the first year of use. 'Perfect Use' corresponds to the method effectiveness in optimal conditions, and 'Typical Use' refers to the efficacy among typical users. The efficacy and adherence at 1 year of use were obtained from studies performed in adult women.

available, inexpensive, and easy to use without systemic effects. However, when condoms are used as the only contraceptive method, an unacceptably high rate of pregnancy is observed. For these reasons, it is recommended that adolescents use both a barrier method and hormonal contraception that offers both contraception and protection against sexually transmitted infections (76, 80).

Although IUDs are frequently used in adult women, they are rarely used by adolescents. The American Academy of Pediatrics states that an IUD may be an appropriate alternative for adolescents who have already had an unintended pregnancy using another method (76).

Hormonal contraception

Hormonal contraception, one of the most efficient methods, is less frequently used in women with T1D and type 2 diabetes in comparison to women without diabetes (85–88). Social support and positive attitudes toward birth control are factors associated with the correct use and good compliance of oral contraception in these patients (89).

Hormonal methods include preparations with ethinyl-estradiol (EE) and a progestin (combined contraceptives) or preparations that contain progestin only, which can be administered in different forms (Table 3). All progestins have progestogenic, antigonadotropic, and antiestrogenic effects, but they also act on other steroidal receptors and exhibit different biological effects (Table 4) (90).

The use of combined low-dose oral contraceptives (OCs), which corresponds to products containing less than 50 μg of EE, has been reported by 20–57% of healthy adolescents. Other popular contraceptives in healthy adolescents in the USA are injectable hormonal methods, which have progressively increased 15–23% in use (72, 76, 84). The progestin-only pills are rarely recommended for young women because of an unacceptable failure rate when administered orally. Reduced bone mineral density has been reported in adolescents using depot medroxyprogesterone acetate, and this method is not recommended for adolescents with T1D (91–93). This side effect has not been shown

Table 4. Types of progestins used in combined oral contraceptives

Type of progestin	Androgen receptor	Glucocorticoid receptor	Mineralocorticoid receptor	Clinical signs/symptoms that may be observed associated with the biological effect on other steroidal receptors
Natural progesterone	−	+	−−	
Derived from testosterone				
First generation:				
Norethisterone, norethindrone	+			Acne, spotting, headache, weight gain, breast tenderness, nausea
Second generation:				
Levonorgestrel, norgestrel	+			Acne, headache, weight gain, breast tenderness, nausea
Third generation:				
Desogestrel, etonogestrel	+			Headache, weight gain, breast tenderness, nausea
Gestodene	+	++	−−−	Headache, weight gain, breast tenderness, nausea
Norgestimate*, norelgestromin	+			Nausea, weight change, spotting, breast tenderness
Fourth generation:				
Dienogest†	−−			Breast tenderness, depression, headache
Derived from progesterone				
Chlormadinone acetate	−	+		Depression, fatigue, weight gain, headache
Cyproterone acetate	−−−	+		Depression, fatigue, weight gain
Medroxyprogesterone acetate	+	++	−	Weight gain, depression, reduced bone mass
Derived from spironolactone				
Drospirenone	−		−−−	Headache, spotting, breast tenderness, depression

Effects on other steroidal receptors and the clinical effects secondary to the binding of these progestins to these receptors are shown. The magnitude of agonist action is shown with a '+' sign and a '−' sign is shown for antagonist effect. The intensity of the agonist effect is shown as +: mild, ++: moderate, +++: intense. The magnitude of the antagonist action is shown as −: mild, −−: moderate, −−−: intense.

*Norgestimate is included in the second generation, although it is a 'new' progestin because its activity is a result of levonorgestrel and levonorgestrel metabolites.

†Dienogest is a hybrid progestin because it has the chemical structure of 19-nortestosterone derivatives but also has characteristics of progesterone derivatives, such as antiandrogenic activity.

for the levonorgestrel implant. We would like to highlight that the safest choice for teens is a combination method that includes condoms.

Side effects of oral contraceptives

Studies performed in healthy women over the last 50 years have shown that OCs are effective and are not associated with significant long-term adverse events (94). One concern regarding the use of OCs during adolescence is the attainment of normal bone mass, which is critical during the second decade of life. Several studies have shown that users of OC on 30 μg of EE achieved a normal increase in bone mass (95). However, some studies have shown potential negative effects with lower estrogen doses. Therefore, it is our opinion that formulations containing 20 and 15 μg of EE are not advised for young patients with T1D who are prone to osteopenia (95, 96). Additional concerns regarding infertility or breast cancer among individuals that have used OCs for more than 8 years or started younger than 20 years of age were not supported by a large population-based study (94).

Numerous studies have evaluated the side effects of OCs in healthy women, but few studies have evaluated this issue in patients with T1D. Visser et al. reviewed the available literature regarding hormonal and nonhormonal contraceptives in women with T1D and type 2 diabetes (97). The authors only found two randomized studies performed in women with T1D that fulfilled the criteria for inclusion (98, 99), although there are two additional case-control studies that studied OC in patients with T1D (100, 101).

The side effects of hormonal contraceptives typically include weight gain, influence on glucose and insulin metabolism, an altered lipid profile, and cardiovascular complications. Healthy adolescents apparently do not experience weight gain associated with OC, although some studies describe a mild effect on this anthropometric variable (76, 102). The four studies mentioned previously did not indicate a significant effect on weight in women with T1D (98–101).

The effects of OC on metabolic control have not been widely studied, although effects ranging from none to mild have been described on glucose levels and insulin requirements. A study performed in rats with streptozotocin-induced diabetes treated with OCs showed no significant differences in blood sugar levels, glycosylated hemoglobin, and plasma insulin levels (103). In the 1980s, Skouby did not observe an effect of such treatments on plasma glucose and insulin requirements in patients with T1D. However, using a high dose of 50 μg of EE, Radberg et al. demonstrated an increase in the daily insulin dose requirements. Diab et al. prospectively studied 80 women with diabetes and treated those with an HbA1c lower than 8% with OC, levonorgestrel implants, a copper IUD, or depot medroxyprogesterone. The OC and depot medroxyprogesterone groups showed a mild increase of 10 mg/dL in fasting blood glucose without significant changes in the daily insulin dose (100).

Healthy women and women with T1D treated with OCs exhibited an increase in triglycerides and HDL levels (98–101). However, Diab et al. showed that treatment with levonorgestrel implants did not adversely affect the lipid profile and that treatment with depot medroxyprogesterone acetate was associated with elevations in total and LDL cholesterol and decreases in HDL cholesterol (100). These data suggest that either OC or levonorgestrel implants, but not depot medroxyprogesterone, may be used in patients with T1D.

The effects of OC on micro- and macrovascular disease are unclear. Although the use of low-dose OC seems to have a positive effect on preventing the appearance of early stages of macrovascular disease (21, 104, 105), the use of high dose EE during the 1970s was associated with a negative effect (106). This concern arises from the fact that high estrogen environments, as seen during pregnancy, are associated with detrimental effects leading to vascular complications in women with T1D. More recent studies using low doses of EE have not shown detrimental effects on micro- and macrovascular complications (107–109). However, the WHO does not recommend OC for women who already have these complications.

Some of the most severe secondary effects of OC are thrombotic events because of alterations in endothelial function, venous stasis and procoagulant changes in blood proteins. However, this risk does not appear to increase in women with T1D (97), which can be explained by a simultaneous increase in the procoagulant state and the fibrinolytic system (110, 111).

In summary, several alternatives to OC, including different estrogen doses and types of progestin, are available for adolescents. OCs with 30 μg of EE may be used in adolescents with T1D, but we do not advise lower doses of estrogen. The optimal type of progestin is not clear for girls with T1D. Levonorgestel implants may be used, but we do not recommend depot medroxyprogesterone in these patients. Additionally, a barrier method should be recommended to prevent sexually transmitted diseases. However, little information exists to reach clear conclusions about the side effects of OC and the best choice of progestin in adolescents with T1D.

Pregnancy in adolescents with T1D: diabetes care during an unplanned pregnancy

Maternal hyperglycemia during pregnancy is harmful for both mother and fetus. Prepregnancy care with

improved glycemic control in early pregnancy is associated with a significant reduction in malformation, stillbirth, neonatal death, and premature delivery (112, 113). Raising awareness about these risks and the importance of preventing an unplanned pregnancy through preconception counseling for teens with diabetes has been shown to be effective (77, 78).

Maternal and fetal complications of T1D during pregnancy are described in Table 5. A higher incidence of polyhydramnios and hypertensive disorders and progression of diabetes-related chronic complications are the main maternal problems observed in pregnant patients with T1D, even if they have good metabolic control (114, 115). There is a 3–5-fold risk of preterm delivery, including spontaneous and indicated premature delivery, in women with pregestational diabetes (116, 117). The risks of stillbirth and major malformations in the pregnancies of patients with T1D are about three and eight times higher than in pregnancies uncomplicated by diabetes, respectively (114, 116, 118). Major malformations are caused by hyperglycemia during the first 8 weeks of gestation and account for 50% of perinatal mortality (119–121). Fetal complications later in the pregnancy arise from fetal hyperinsulinemia secondary to maternal hyperglycemia, leading to macrosomia (122–124).

Most pregnancies in adolescents with T1D are unplanned. Folic acid at a dose of 1–5 mg/day should be administered immediately upon diagnosis of an unplanned pregnancy (125, 126), and an early ultrasonogram should be performed to evaluate gestational age along with early screening for thyroid dysfunction (Table 6). Withdrawal of medications that cannot be used during pregnancy should be considered. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists should be stopped because of concerns about an association with renal failure in the fetus, oligohydramnios and skeletal malformations (127–129). Because there is some evidence, although contradictory, for advising the withdrawal of diuretics and statins during pregnancy, they should be discontinued until more information is available (130–132).

Caring for pregnant adolescents with T1D includes aspects related to achieving optimal metabolic control, the type of insulin treatment used and screening for the presence of complications. To achieve optimal glucose levels, the number of finger-stick blood glucose measurements should be increased to 6–8 times per day (fasting, pre-meal, postprandial, and at bedtime) (133). The target glucose levels should be modified according to recommendations for pregnant women. Fasting and pre-meal blood glucose levels should be in the 60–90 mg/dL range. The target level for postprandial glucose has been a matter of debate, and 1-h postprandial glucose levels between 100 and 129 mg/dL are recommended (134). Close follow-up of the patients should be performed, and medical visits should be scheduled every 1–2 weeks.

Table 5. Adverse pregnancy outcomes in pregnancies in women with type 1 diabetes (T1D)

Maternal
First trimester abortion
Stillbirth
Pregnancy-induced hypertension (preeclampsia)
Infection
Premature delivery
Higher rate of cesarean section
Fetal and Neonatal
First trimester abortion
Stillbirth
Intrauterine growth retardation
Macrosomia
Polyhydramnios
Premature delivery
Shoulder dystocia
Fetal hypoxia
Neonatal pulmonary distress
Hypoglycemia
Hypocalcemia
Polycythemia
Neonatal jaundice
Congenital malformations:
Neurologic: Anencephaly, myelomeningocele, holoprosencephaly, microcephaly
Skeletal: Caudal regression defects (sirenomelia, sacral agenesis, caudal agenesis, imperforate anus)
Cardiovascular: Fetal hypertrophic cardiomyopathy, double outlet right ventricle, ventricular septal defects, transposition of the great arteries, patent ductus arteriosus, pulmonary stenosis
Genitourinary: Ureter duplication, renal agenesis, hypospadias

Pregnancy may accelerate chronic complications, and adolescents with unplanned pregnancies should be screened for retinopathy and nephropathy (115, 135). A recent study performed in 102 pregnant women with diabetes with an initial HbA1c level of 6.7% showed that progression of retinopathy occurred in 27% of the women (136). Similarly, nephropathy may also be accelerated during pregnancy, but microalbuminuria may revert after delivery. Nephropathy is associated with an increased risk of preeclampsia, nephrotic syndrome, preterm delivery, fetal growth restriction, and perinatal mortality (137).

Changes in insulin therapy during pregnancy are frequently performed, including changes in insulin dose and type. Human insulin, lispro, and aspart have been approved for use during pregnancy with a Federal Drug Administration (FDA) category of B (138), but there is no published data on the use of glulisine in pregnancy. Insulin lispro was the first insulin analog used for the care of diabetes in pregnant women (139). Several studies have shown that this analog used at normal doses does not cross the placenta into the fetus

Table 6. Recommendations for management of unplanned pregnancy in adolescents with type 1 diabetes

First trimester
Folic acid 5 mg/day (1–5 mg/day)
Withdrawal some drugs: angiotensin-converting enzyme inhibitors, angiotensin receptor antagonist, statins, diuretics
Evaluate thyroid hormone levels
Refer to a high-risk obstetric unit
Perform an early ultrasonogram
Diabetes care:
Screen for retinopathy and nephropathy
Consider changes in the type of insulin, with a preference for aspart, lispro, and NPH insulin
Intensify diabetes treatment. Medical control of diabetes once or twice monthly
Increase the number of glucose levels tests to 6–8 times by day
Change the targets of metabolic control: fasting and pre-meal capillary glucose level of 60–90 mg/dL and 1-h postprandial glucose levels of 100–129 mg/dL
Second trimester
Anatomic ultrasound at 20–22 weeks
Consider hospital admission in cases of poor metabolic control, worsening of maternal pathologies, or deterioration of the fetoplacental unit
Third trimester
Weekly medical control
From 32 weeks onward, perform a weekly or twice weekly biophysical profile and basal monitoring of fetal wellbeing
Interruption of pregnancy:
At 38 weeks, if the metabolic control is good, without maternal or fetal complications
At 36 weeks, in pregnancies with micro- or macrovascular complications
Induce fetal lung maturity if delivery is to be performed earlier than term

and is safe for the treatment of women with T1D (140). In a retrospective analysis of 500 pregnancies in which the women were treated with insulin lispro before and during organogenesis, 5.4% experienced congenital anomalies; however, this complication only occurred in pregnancies with very high A1C levels (141). Similarly, a good fetal outcome was described for aspart insulin compared to human insulin with a tendency toward fewer fetal losses and preterm deliveries (142). When available, pump therapy before pregnancy is the most flexible and rapidly adjustable way to manage diabetes during pregnancy for patients with T1D (143).

Currently, the only accepted basal insulin for use during pregnancy is neutral protamine Hagedorn (NPH) insulin (144), but future approval of basal analogs is anticipated. Although no results from randomized clinical trials using glargine during pregnancy are currently available, retrospective and case-control studies have shown that pregnancies with T1D demonstrated an incidence of congenital malformation similar to that observed with human insulin (145). Insulin glargine does not cross the placenta (146). Similarly, there are no clinical studies of insulin detemir in pregnant women with diabetes, but the results of a prospective study are expected in late 2011.

The ACOG recommends that obstetric control should be performed in a high-risk obstetric unit twice a month until the third trimester (28 weeks of gestation) and then weekly until delivery (147). An early ultrasound should be performed to certify the gestational age, number of fetuses and fetal viability (148). An anatomic ultrasound should be performed at 20–22 weeks of gestation to detect congenital malformations along with a maternal Doppler at 22 weeks to detect the risk of preeclampsia and preterm delivery (147, 149). A biophysical profile and basal monitoring should be performed weekly from 32 weeks or twice a week when additional pathologies are present (150). Daily fetal movement counts should be performed, and hospital admission should be considered in cases of poor metabolic control, associated maternal pathologies, worsening of renal function, or deterioration of the fetoplacental unit (151).

Although experts recommend considering elective interruption at 38 weeks if the mother has good metabolic control and in an absence of maternal or fetal complications, there is little evidence to support that this approach decreases maternal and perinatal morbidity and mortality if the antenatal surveillance is reassuring (147, 152). An earlier interruption, at 36 weeks, is recommended in pregnancies with micro- or macrovascular complications. It is important to assess or induce fetal lung maturity if delivery is to be performed before 39 weeks of gestation (147, 151).

We conclude that an unplanned pregnancy in an adolescent with T1D is a serious condition that requires a rapid and complete clinical evaluation to detect chronic complications and intensification of insulin therapy to achieve optimal metabolic control.

Final conclusions

The manifestations of T1D on pubertal development have dramatically changed during the last 50 years. The

age of menarche in patients with T1D has followed the secular trend toward an earlier age similar to the general population. However, a small delay in the age of menarche still occurs in these patients. Menstrual abnormalities are a prevalent problem for adolescents with T1D, but ovulatory function is not impaired. Ovulatory cycles may be observed in girls with insufficient metabolic control and menstrual irregularities. These data highlight the importance of pregnancy prevention in girls with T1D. Therefore, diabetes care of the adolescent with T1D should include education and promotion of contraception in order to achieve a decrease in unplanned pregnancies in these patients.

The scarcity of studies regarding contraception and pregnancy during adolescence suggests that new and updated research about these issues in adolescents with T1D is needed. Future studies evaluating new drugs and delivery routes for hormonal contraception are needed to increase the knowledge base for choosing a specific contraceptive method for girls with T1D. Similarly, more research is needed to manage unplanned pregnancies in adolescents with T1D.

Acknowledgements

We thank all the health professionals who have collaborated in our studies, and we are especially grateful to all the subjects for their participation. This work was funded by Fondo Nacional de Ciencia y Tecnología (FONDECYT) Grants 1100123 and 1050452.

References

1. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 2003: 24: 668–693.
2. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med 1982: 306: 1033–1035.
3. Aksglaede L, Sorensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen puberty study. Pediatrics 2009: 123: e932–e939.
4. Herman-Giddens ME, Slora EJ, Wasserman RC et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in office settings network. Pediatrics 1997: 99: 505–512.
5. Codner E, Unanue N, Gaete X et al. Age of pubertal events in Chilean school age girls and its relationship with socioeconomic status and body mass index. Rev Med Chil 2004: 132: 801–808.
6. Bergqvist N. The gonadal function in female diabetics. Acta Endocrinol Suppl (Copenh) 1954: 19: 1–20.
7. Mauriac P. Gros ventre, hepatomegalie, troubles de la croissance chez les enfants diabetiques, traites depuis plusieury annes par l'insuline. Gaz Hebd Sci Med Bordeaux 1930: 51: 402.
8. Codner E, Barrera A, Mook-Kanamori D et al. Ponderal gain, waist-to-hip ratio, and pubertal development in girls with type-1 diabetes mellitus. Pediatr Diabetes 2004: 5: 182–189.
9. Rohrer T, Stierkorb E, Heger S et al. Delayed pubertal onset and development in German children and adolescents with type 1 diabetes: cross-sectional analysis of recent data from the DPV diabetes documentation and quality management system. Eur J Endocrinol 2007: 157: 647–653.
10. Codner E, Cassorla F. Puberty and ovarian function in girls with type 1 diabetes mellitus. Horm Res 2009: 71: 12–21.
11. Danielson KK, Palta M, Allen C, D'Alessio DJ. The association of increased total glycosylated hemoglobin levels with delayed age at menarche in young women with type 1 diabetes. J Clin Endocrinol Metab 2005: 90: 6466–6471.
12. Picardi A, Cipponeri E, Bizzarri C, Fallucca S, Guglielmi C, Pozzilli P. Menarche in type 1 diabetes is still delayed despite good metabolic control. Fertil Steril 2008: 90: 1875–1877.
13. Strotmeyer ES, Steenkiste AR, Foley TP Jr, Berga SL, Dorman JS. Menstrual cycle differences between women with type 1 diabetes and women without diabetes. Diabetes Care 2003: 26: 1016–1021.
14. Schweiger B, Klingensmith GJ, Snell-Bergeon JK. Menarchal timing in type 1 diabetes through the last 4 decades. Diabetes Care 2010: 33: 2521–2523.
15. Deltsidou A. Age at menarche and menstrual irregularities of adolescents with type 1 diabetes. J Pediatr Adolesc Gynecol 2010: 23: 162–167.
16. Lombardo F, Salzano G, Crisafulli G et al. Menarcheal timing in intensively treated girls with type 1 diabetes mellitus. Nutr Metab Cardiovasc Dis 2009: 19: 35–38.
17. Kjaer K, Hagen C, Sando SH, Eshoj O. Epidemiology of menarche and menstrual disturbances in an unselected group of women with insulin-dependent diabetes mellitus compared to controls. J Clin Endocrinol Metab 1992: 75: 524–529.
18. Yeshaya A, Orvieto R, Dicker D, Karp M, Ben-Rafael Z. Menstrual characteristics of women suffering from insulin-dependent diabetes mellitus. Int J Fertil Menopausal Stud 1995: 40: 269–273.
19. Anai T, Miyazaki F, Tomiyasu T, Matsuo T. Risk of irregular menstrual cycles and low peak bone mass during early adulthood associated with age at menarche. Pediatr Int 2001: 43: 483–488.
20. Codner E. Estrogen and type 1 diabetes mellitus. Pediatr Endocrinol Rev 2008: 6: 228–234.
21. Snell-Bergeon JK, Dabelea D, Ogden LG et al. Reproductive history and hormonal birth control use are associated with coronary calcium progression in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 2008: 93: 2142–2148.
22. Adcock CJ, Perry LA, Lindsell DR et al. Menstrual irregularities are more common in adolescents with type 1 diabetes: association with poor glycaemic control and weight gain. Diabet Med 1994: 11: 465–470.
23. Schroeder B, Hertweck SP, Sanfilippo JS, Foster MB. Correlation between glycemic control and menstruation in diabetic adolescents. J Reprod Med 2000: 45: 1–5.

24. 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 2010: 94: 1822–1826.
25. Deltsidou A, Lemonidou C, Zarikas V, Matziou V, Bartsocas CS. Oligomenorrhoea in adolescents with type 1 diabetes mellitus: relationship to glycaemic control. Eur J Obstet Gynecol Reprod Biol 2010: 153: 62–66.
26. ACOG Committee Opinion No. 349. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Obstet Gynecol 2006: 108: 1323–1328.
27. American Academy of Pediatrics, Committee on Adolescence, American College of Obstetricians and Gynecologists, Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006: 118: 2245–2250.
28. Southam AL. The natural history of menstrual disorders. Ann N Y Acad Sci 1959: 75: 840–854.
29. World Health Organization multicenter study on menstrual and ovulatory patterns in adolescent girls. II. Longitudinal study of menstrual patterns in the early postmenarcheal period, duration of bleeding episodes and menstrual cycles. World Health Organization Task Force on Adolescent Reproductive Health. J Adolesc Health Care 1986: 7: 236–244.
30. Adams Hillard PJ. Menstruation in adolescents: what's normal, what's not. Ann N Y Acad Sci 2008: 1135: 29–35.
31. Codner E, Soto N, Lopez P et al. Diagnostic criteria for polycystic ovary syndrome and ovarian morphology in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 2006: 91: 2250–2256.
32. Escobar-Morreale HF, Roldan B, Barrio R et al. High prevalence of the polycystic ovary syndrome and hirsutism in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 2000: 85: 4182–4187.
33. Willis D, Mason H, Gilling-Smith C, Franks S. Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries. J Clin Endocrinol Metab 1996: 81: 302–309.
34. Poretsky L, Cataldo NA, Rosenwaks Z, Giudice LC. The insulin-related ovarian regulatory system in health and disease. Endocr Rev 1999: 20: 535–582.
35. Azziz R, Carmina E, Dewailly D et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2008: 91: 456–488.
36. Malcolm CE, Cumming DC. Does anovulation exist in eumenorrheic women? Obstet Gynecol 2003: 102: 317–318.
37. Codner E, Eyzaguirre FC, Iniguez G et al. Ovulation rate in adolescents with type 1 diabetes mellitus. Fertil Steril 2011: 95: 197–202.
38. Hargreave TB, Mills JA. Investigating and managing infertility in general practice. BMJ 1998: 316: 1438–1441.
39. Healy DL, Trounson AO, Andersen AN. Female infertility: causes and treatment. Lancet 1994: 343: 1539–1544.
40. Thonneau P, Marchand S, Tallec A et al. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Hum Reprod 1991: 6: 811–816.
41. Steel JM, Johnstone SD, Corrie JE. Early assessment of gestation in diabetics. Lancet 1984: 2: 975–976.
42. Djursing H, Hagen C, Nyboe Andersen A, Svenstrup B, Bennett P, Molsted Pedersen L. Serum sex hormone concentrations in insulin dependent diabetic women with and without amenorrhoea. Clin Endocrinol (Oxf) 1985: 23: 147–154.
43. Griffin ML, South SA, Yankov VI et al. Insulin-dependent diabetes mellitus and menstrual dysfunction. Ann Med 1994: 26: 331–340.
44. Bestetti GE, Junker U, Locatelli V, Rossi GL. Continuous subtherapeutic insulin counteracts hypothalamopituitary-gonadal alterations in diabetic rats. Diabetes 1987: 36: 1315–1319.
45. Bruning JC, Gautam D, Burks DJ et al. Role of brain insulin receptor in control of body weight and reproduction. Science 2000: 289: 2122–2125.
46. Castellano JM, Navarro VM, Fernandez-Fernandez R et al. Expression of hypothalamic KiSS-1 system and rescue of defective gonadotropic responses by kisspeptin in streptozotocin-induced diabetic male rats. Diabetes 2006: 55: 2602–2610.
47. Castellano JM, Navarro VM, Roa J et al. Alterations in Hypothalamic KiSS-1 System in Experimental Diabetes: Early Changes and Functional Consequences. Endocrinology 2009: 150: 784–794.
48. Castellano JM, Navarro VM, Fernandez-Fernandez R et al. Changes in hypothalamic KiSS-1 system and restoration of pubertal activation of the reproductive axis by kisspeptin in undernutrition. Endocrinology 2005: 146: 3917–3925.
49. Codner E, Escobar-Morreale HF. Clinical review: hyperandrogenism and polycystic ovary syndrome in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 2007: 92: 1209–1216.
50. Codner E, Iniguez G, Hernandez IM et al. Elevated anti-Mullerian hormone (AMH) and inhibin B levels in prepubertal girls with type 1 diabetes mellitus. Clin Endocrinol (Oxf) 2011: 74: 73–78.
51. Remer T, Maser-Gluth C, Boye KR, Hartmann MF, Heinze E, Wudy SA. Exaggerated adrenarche and altered cortisol metabolism in Type 1 diabetic children. Steroids 2006: 71: 591–598.
52. Pillion DJ, Arnold P, Yang M, Stockard CR, Grizzle WE. Receptors for insulin and insulin-like growth factor-I in the human adrenal gland. Biochem Biophys Res Commun 1989: 165: 204–211.
53. Polderman KH, Gooren LJ, Heine RJ. Effects of physiological and supraphysiological doses of insulin on adrenal androgen levels. Horm Metab Res 1996: 28: 152–155.
54. Codner E, Mook-Kanamori D, Bazaes RA et al. Ovarian function during puberty in girls with type 1 diabetes mellitus: response to leuprolide. J Clin Endocrinol Metab 2005: 90: 3939–3945.
55. Meyer K, Deutscher J, Anil M, Berthold A, Bartsch M, Kiess W. Serum androgen levels in adolescents with type 1 diabetes: relationship to pubertal stage and metabolic control. J Endocrinol Invest 2000: 23: 362–368.
56. Virdis R, Zampolli M, Street ME et al. Ovarian 17 alpha-hydroxyprogesterone responses to GnRH

analog testing in oligomenorrheic insulin-dependent diabetic adolescents. Eur J Endocrinol 1997: 136: 624–629.
57. Roldan B, Escobar-Morreale HF, Barrio R et al. Identification of the source of androgen excess in hyperandrogenic type 1 diabetic patients. Diabetes Care 2001: 24: 1297–1299.
58. Codner E, Iniguez G, Villarroel C et al. Hormonal profile in women with polycystic ovarian syndrome with or without type 1 diabetes mellitus. J Clin Endocrinol Metab 2007: 92: 4742–4746.
59. Bolli GB. Physiological insulin replacement in type 1 diabetes mellitus. Exp Clin Endocrinol Diabetes 2001: 109(Suppl 2): S317–S332.
60. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev 1987: 8: 132–141.
61. Kezele PR, Nilsson EE, Skinner MK. Insulin but not insulin-like growth factor-1 promotes the primordial to primary follicle transition. Mol Cell Endocrinol 2002: 192: 37–43.
62. Sir-Petermann T, Codner E, Maliqueo M et al. Increased anti-mullerian hormone serum concentrations in prepubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006: 91: 3105–3109.
63. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care 1990: 13: 610–630.
64. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997: 18: 774–800.
65. Diamanti-Kandarakis E, Piperi C, Patsouris E et al. Immunohistochemical localization of advanced glycation end-products (AGEs) and their receptor (RAGE) in polycystic and normal ovaries. Histochem Cell Biol 2007: 127: 581–589.
66. Soto N, Iniguez G, Lopez P et al. Anti-mullerian hormone and inhibin B levels as markers of premature ovarian aging and transition to menopause in type 1 diabetes mellitus. Hum Reprod 2009: 24: 2838–2844.
67. Dorman JS, Steenkiste AR, Foley TP et al. Menopause in type 1 diabetic women: is it premature? Diabetes 2001: 50: 1857–1862.
68. Chang AS, Dale AN, Moley KH. Maternal diabetes adversely affects preovulatory oocyte maturation, development, and granulosa cell apoptosis. Endocrinology 2005: 146: 2445–2453.
69. Colton SA, Pieper GM, Downs SM. Altered meiotic regulation in oocytes from diabetic mice. Biol Reprod 2002: 67: 220–231.
70. Court JM, Cameron FJ, Berg-Kelly K, Swift PG. Diabetes in adolescence. Pediatr Diabetes 2008: 9: 255–262.
71. Standards of medical care in diabetes – 2010. Diabetes Care 2010: 33(Suppl 1): S11–S61.
72. Charron-Prochownik D, Sereika SM, Falsetti D et al. Knowledge, attitudes and behaviors related to sexuality and family planning in adolescent women with and without diabetes. Pediatr Diabetes 2006: 7: 267–273.
73. Martinez-Aguayo A, Araneda JC, Fernandez D, Gleisner A, Perez V, Codner E. Tobacco, alcohol, and illicit drug use in adolescents with diabetes mellitus*. Pediatr Diabetes 2007: 8: 265–271.
74. 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 2006: 32: 235–242.
75. Committee on Psychosocial Aspects of Child and Family Health and Committee on Adolescence. Sexuality education for children and adolescents. Pediatrics 2001: 108: 498–502.
76. Blythe MJ, Diaz A. Contraception and adolescents. Pediatrics 2007: 120: 1135–1148.
77. Charron-Prochownik D, Ferons-Hannan M, Sereika S, Becker D. Randomized efficacy trial of early preconception counseling for diabetic teens (READY-girls). Diabetes Care 2008: 31: 1327–1330.
78. Fischl AF, Herman WH, Sereika SM et al. Impact of a preconception counseling program for teens with type 1 diabetes (READY-Girls) on patient-provider interaction, resource utilization, and cost. Diabetes Care 2010: 33: 701–705.
79. Oringanje C, Meremikwu MM, Eko H, Esu E, Meremikwu A, Ehiri JE. Interventions for preventing unintended pregnancies among adolescents. Cochrane Database Syst Rev 2009: CD005215.
80. Weisberg E. Contraceptive options for women in selected circumstances. Best Pract Res Clin Obstet Gynaecol 2010: 24: 593–604.
81. Hillman JB, Negriff S, Dorn LD. Perceived competence and contraceptive use during adolescence. Contraception 2010: 81: 249–253.
82. WHO Medical Eligibility Criteria for Contraceptive Use, 4th edn., 2009.
83. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL et al. Type of contraception method used at last intercourse and associations with health risk behaviors among US adolescents. Contraception 2010: 82: 549–555.
84. Vital signs: teen pregnancy – United States, 1991 – 2009. MMWR Morb Mortal Wkly Rep 2011: 60: 414–420.
85. Falsetti D, Charron-Prochownik D, Serelka S et al. Condom use, pregnancy, and STDs in adolescent females with and without type 1 diabetes. Diabetes Educ 2003: 29: 135–143.
86. Shawe J, Mulnier H, Nicholls P, Lawrenson R. Use of hormonal contraceptive methods by women with diabetes. Prim Care Diabetes 2008: 2: 195–199.
87. 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 1999: 16: 395–399.
88. 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 2001: 99: 232–237.
89. St James PJ, Younger MD, Hamilton BD, Waisbren SE. Unplanned pregnancies in young women with diabetes. An analysis of psychosocial factors. Diabetes Care 1993: 16: 1572–1578.
90. Schindler AE, Campagnoli C, Druckmann R et al. Classification and pharmacology of progestins. Maturitas 2008: 61: 171–180.
91. Cromer BA, Bonny AE, Stager M et al. Bone mineral density in adolescent females using injectable or

oral contraceptives: a 24-month prospective study. Fertil Steril 2008: 90: 2060–2067.
92. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adolesc Med 2005: 159: 139–144.
93. Harel Z, Johnson CC, Gold MA et al. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. Contraception 2010: 81: 281–291.
94. Marchbanks PA, McDonald JA, Wilson HG et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002: 346: 2025–2032.
95. Agostino H, Di Meglio G. Low-dose oral contraceptives in adolescents: how low can you go?. J Pediatr Adolesc Gynecol 2010: 23: 195–201.
96. Soto N, Pruzzo R, Eyzaguirre F et al. Bone mass and sex steroids in postmenarcheal adolescents and adult women with Type 1 diabetes mellitus. J Diabetes Complications 2011: 25: 19–24.
97. 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 2006: CD003990.
98. Radberg T, Gustafson A, Skryten A, Karlsson K. Oral contraception in diabetic women. A cross-over study on serum and high density lipoprotein (HDL) lipids and diabetes control during progestogen and combined estrogen/progestogen contraception. Horm Metab Res 1982: 14: 61–65.
99. Skouby SO, Molsted-Pedersen L, Kuhl C, Bennet P. Oral contraceptives in diabetic women: metabolic effects of four compounds with different estrogen/progestogen profiles. Fertil Steril 1986: 46: 858–864.
100. Diab KM, Zaki MM. Contraception in diabetic women: comparative metabolic study of Norplant, depot medroxyprogesterone acetate, low dose oral contraceptive pill and CuT380A. J Obstet Gynaecol Res 2000: 26: 17–26.
101. Petersen KR, Skouby SO, Vedel P, Haaber AB. Hormonal contraception in women with IDDM. Influence on glycometabolic control and lipoprotein metabolism. Diabetes Care 1995: 18: 800–806.
102. Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database Syst Rev 2008: CD003987.
103. Adeghate E. Effect of oral contraceptive steroid hormones on metabolic parameters of streptozotocin-induced diabetic rat. Contraception 2000: 62: 327–329.
104. Sidney S, Siscovick DS, Petitti DB et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998: 98: 1058–1063.
105. Klein BE, Klein R, Moss SE. Mortality and hormone-related exposures in women with diabetes. Diabetes Care 1999: 22: 248–252.
106. Steel JM, Duncan LJ. Serious complications of oral contraception in insulin-dependent diabetics. Contraception 1978: 17: 291–295.
107. Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE. Oral contraceptives and renal and retinal complications in young women with insulin-dependent diabetes mellitus. JAMA 1994: 271: 1099–1102.
108. Klein BE, Klein R, Moss SE. Exogenous estrogen exposures and changes in diabetic retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 1999: 22: 1984–1987.
109. Napoli A, Colatrella A, Botta R et al. Contraception in diabetic women: an Italian study. Diabetes Res Clin Pract 2005: 67: 267–272.
110. Petersen KR, Skouby SO, Sidelmann J, Jespersen J. Assessment of endothelial function during oral contraception in women with insulin-dependent diabetes mellitus. Metabolism 1994: 43: 1379–1383.
111. Petersen KR, Skouby SO, Jespersen J. Balance of coagulation activity with fibrinolysis during use of oral contraceptives in women with insulin-dependent diabetes mellitus. Int J Fertil Menopausal Stud 1995: 40(Suppl 2): 105–111.
112. Temple RC, Aldridge VJ, Murphy HR. Prepregnancy care and pregnancy outcomes in women with type 1 diabetes. Diabetes Care 2006: 29: 1744–1749.
113. Murphy HR, Roland JM, Skinner TC et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes. Diabetes Care 2010: 33: 2514–2520.
114. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004: 328: 915.
115. Kaaja R. Vascular complications in diabetic pregnancy. Thromb Res 2011: 127(Suppl 3): S53–S55.
116. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diabetes Care 2009: 32: 2005–2009.
117. Sibai BM, Caritis SN, Hauth JC et al. Preterm delivery in women with pregestational diabetes mellitus or chronic hypertension relative to women with uncomplicated pregnancies. The National Institute of Child Health and Human Development Maternal – Fetal Medicine Units Network. Am J Obstet Gynecol 2000: 183: 1520–1524.
118. Dunne FP, Avalos G, Durkan M et al. ATLANTIC DIP: pregnancy outcome for women with pregestational diabetes along the Irish Atlantic seaboard. Diabetes Care 2009: 32: 1205–1206.
119. Jensen DM, Korsholm L, Ovesen P et al. Periconceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. Diabetes Care 2009: 32: 1046–1048.
120. Temple R, Aldridge V, Greenwood R, Heyburn P, Sampson M, Stanley K. Association between outcome of pregnancy and glycaemic control in early pregnancy in type 1 diabetes: population based study. BMJ 2002: 325: 1275–1276.
121. Nielsen GL, Moller M, Sorensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. Diabetes Care 2006: 29: 2612–2616.
122. Metzger BE, Persson B, Lowe LP et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. Pediatrics 2010: 126: e1545–e1552.

123. Metzger BE, Lowe LP, Dyer AR et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008: 358: 1991–2002.
124. Lindsay RS, Hamilton BA, Calder AA, Johnstone FD, Walker JD. The relation of insulin, leptin and IGF-1 to birthweight in offspring of women with type 1 diabetes. Clin Endocrinol (Oxf) 2004: 61: 353–359.
125. Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. QJM 2001: 94: 435–444.
126. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD. Preconception care of diabetes. Glycemic control prevents congenital anomalies. JAMA 1991: 265: 731–736.
127. Cooper WO. Clinical implications of increased congenital malformations after first trimester exposures to angiotensin-converting enzyme inhibitors. J Cardiovasc Nurs 2008: 23: 20–24.
128. Ray JG, Vermeulen MJ, Koren G. Taking ACE inhibitors during early pregnancy: is it safe? Can Fam Physician 2007: 53: 1439–1440.
129. Cooper WO, Hernandez-Diaz S, Arbogast PG et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006: 354: 2443–2451.
130. Ghanem FA, Movahed A. Use of antihypertensive drugs during pregnancy and lactation. Cardiovasc Ther 2008: 26: 38–49.
131. Churchill D, Beevers GD, Meher S, Rhodes C. Diuretics for preventing pre-eclampsia. Cochrane Database Syst Rev 2007: CD004451.
132. Kazmin A, Garcia-Bournissen F, Koren G. Risks of statin use during pregnancy: a systematic review. J Obstet Gynaecol Can 2007: 29: 906–908.
133. Hone J, Jovanovic L. Approach to the Patient with Diabetes during Pregnancy. J Clin Endocrinol Metab 2010: 95: 3578–3585.
134. Kitzmiller JL, Block JM, Brown FM et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care 2008: 31: 1060–1079.
135. Arun CS, Taylor R. Influence of pregnancy on long-term progression of retinopathy in patients with type 1 diabetes. Diabetologia 2008: 51: 1041–1045.
136. Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes. Diabet Med 2010: 27: 431–435.
137. Howarth C, Gazis A, James D. Associations of type 1 diabetes mellitus, maternal vascular disease and complications of pregnancy. Diabet Med 2007: 24: 1229–1234.
138. Castorino KN, Jovanovic L. Pregnancy and diabetes management: advances and controversies. Clin Chem 2010. DOI: clinchem.2010.155382.
139. Jovanovic L, Ilic S, Pettitt DJ et al. Metabolic and immunologic effects of insulin lispro in gestational diabetes. Diabetes Care 1999: 22: 1422–1427.
140. Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G. Transfer of insulin lispro across the human placenta: in vitro perfusion studies. Diabetes Care 2003: 26: 1390–1394.
141. Wyatt JW, Frias JL, Hoyme HE et al. Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. Diabet Med 2005: 22: 803–807.
142. Hod M, Damm P, Kaaja R et al. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. Am J Obstet Gynecol 2008: 198: 186e1–186e7.
143. Wollitzer AD, Zisser H, Jovanovic L. Insulin pumps and their use in pregnancy. Diabetes Technol Ther 2010: 12(Suppl 1): S33–S36.
144. Torlone E, Di Cianni G, Mannino D, Lapolla A. Insulin analogs and pregnancy: an update. Acta Diabetol 2009: 46: 163–172.
145. Gallen IW, Jaap A, Roland JM, Chirayath HH. Survey of glargine use in 115 pregnant women with Type 1 diabetes. Diabet Med 2008: 25: 165–169.
146. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: a transplacental transfer study. Diabetes Care 2010: 33: 29–33.
147. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 60, March 2005. Pregestational diabetes mellitus. Obstet Gynecol 2005: 105: 675–685.
148. Nizard J, Ville Y. The fetus of a diabetic mother: sonographic evaluation. Semin Fetal Neonatal Med 2009: 14: 101–105.
149. ACOG Practice Bulletin. No. 101: Ultrasonography in pregnancy. Obstet Gynecol 2009: 113: 451–461.
150. ACOG Practice Bulletin. Antepartum fetal surveillance. Number 9, October 1999. Clinical management guidelines for obstetrician-gynecologists (replaces Technical Bulletin 188, January 1994). Int J Gynaecol Obstet 2000: 68: 175–185.
151. Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. Obstet Gynecol 2003: 102: 857–868.
152. Boulvain M, Stan C, Irion O. Elective delivery in diabetic pregnant women. Cochrane Database Syst Rev 2001: CD001997.
153. Díaz E. Breves observaciones sobre la aparicion de la pubertad en la mujer chilena i de las predisposiciones patolójicas propias del sexo. Rev Med Chile. 1888: 16: 289–298, 337–346.
154. Schriock EA, Winter RJ, Traisman HS. Diabetes mellitus and its effects on menarche. J Adolesc Health Care 1984: 5: 101–104.