Long-Acting Contraception in Adolescents and Young Women With Type 1 and Type 2 Diabetes

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REVIEW ARTICLE

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Long-acting contraception in adolescents and young women with type 1 and type 2 diabetes

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Abstract

Adolescent pregnancy is a major public health problem worldwide. Adolescents living with diabetes are not aware of the risks of unplanned pregnancy and the high rate of fetal and maternal complications when gestation occurs in women with significant hyperglycemia. These data highlight the significance of pregnancy prevention in young women with diabetes. Long-acting reversible contraceptives (LARCs), which include subdermal progestin implants and hormonal and nonhormonal intrauterine devices (IUDs), have been recommended by the American College of Obstetricians Gynecologists and the American Academy of Pediatrics as a first-line contraceptive option for adolescents and young women. This article reviews LARC options for adolescents and young women with type 1 (T1D) and type 2 (T2D) diabetes as well as the possible complications and side effects.

KEYWORDS

adolescent, diabetes, IUD, LARC, subdermal implant

1 | INTRODUCTION

Long-acting reversible contraceptives (LARCs) represent a group of methods that are not dependent on user compliance and include intrauterine devices (IUDs) and subcutaneous progestin implants. These methods have the highest contraceptive efficiency among contraceptives, with a pregnancy rate lower than 1% per year.[1]

During the last decade, LARCs have been recommended by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics as a first-line contraceptive option for adolescents and young women.[2-8] The main reasons to recommend LARCs as the first-line choice for adolescents are that they are safe and reversible and have similar pregnancy prevention rates whether they are used perfectly ("*perfect use*") or in a clinical setting ("*typical use*") (Table 1 and Figure 1).[9]

Worldwide, adolescent pregnancy is a major public health problem. Approximately 10% of pregnancies occur in women younger than 20 years. Unfortunately, 25% of maternal and child morbidity and mortality occur in this age group, with high socioeconomic costs to families and society.[10] Unexpectedly, young women with diabetes, who are typically under close medical surveillance, also exhibit a high rate of unintended pregnancy.[11]

Unplanned pregnancy in women with diabetes is associated with a high prevalence of maternal and fetal complications, including stillbirth and major malformations in the newborn.[11-14] These adverse risks are even higher in pregnancies in adolescents with pregestational diabetes, in part due to the worse glycemic control and later attendance of the first medical visit for obstetric care described in adolescents with diabetes.[15] High incidences of major malformations,[11,15] preeclampsia, preterm delivery, high birth weight, and cesarean delivery have been described in teenagers with pregestational diabetes.[11,15] A recent study has also shown more frequent hospital admissions of the offspring of adolescents with type 1 diabetes (T1D) in the first year after delivery.[15] Pregnancy in adolescents with diabetes has a worse outcome than pregnancy in adult women with T1D and in adolescents without diabetes, which highlights the importance of pregnancy prevention in young women with diabetes.[16,17]

Maternal hyperglycemia during pregnancy is harmful to both the mother and the fetus and has a central role in the explanation of complications of pregnancy in women with diabetes. Therefore, the recommendation is to achieve an HbA1c level of ≤6.5% in the months

TABLE 1 Pregnancy rates of the different contraceptive alternatives for adolescents

	Pearl index				
Method	**Perfect use %**	**Typical use %**	**Adherence at 1 year of use %**	**Typical use in adolescents (%)**	**Adherence at 1 year of use in adolescents (%)**
No method	85	85			
Natural methods		20.5-25.0	51		
Calendar	5.0				
Ovulation method	3.0				
Barrier methods					
Male condom	2.0	18.0	53		
Female condom	5.0	21.0	49		
Diaphragm (with spermicides)	6.0	16.0	57		
Sponge (nulliparous)	9.0	24.0	57		
Cervical caps (nulliparous)	9.0	20.0	56		
Spermicides	18.0	28.0	42		
Coitus interruptus	4.0	22.0	no data		
Hormonal methods					
Combined pill	0.1	6.0-8.0	68	5–25	33-38
Progestin-only pill	0.5	3.0	68		
Combined patch	0.5	9.0	68		
Vaginal ring	0.5	9.0	68		
Combined monthly injectable	0.1	6.0	56	0	42-52
Depot medroxiprogesterone acetate	0.3	3.0	56		
Etonogestrel-releasing contraceptive implant	0.05	0.05	84		
Intrauterine devices (IUD)					
Copper T- T380A	0.6	0.8	78	0	42
Levonorgestrel IUD	0.2	0.2	80	0	68

Note: Efficacy is shown as the Pearl Index, which is defined as the number of pregnancies in 100 women during one year of exposure or the proportion of women who experienced an unintended pregnancy within the first year of use. "Perfect Use" corresponds to the method's effectiveness under optimal conditions, and "Typical Use" refers to the efficacy among typical users. Adherence at 1 year of use is obtained from studies performed in adult women; data regarding adherence among adolescents are scarce. Adapted from: WHO., Fifth edition. 2015[52].
Abbreviation: IUD, intrauterine device.

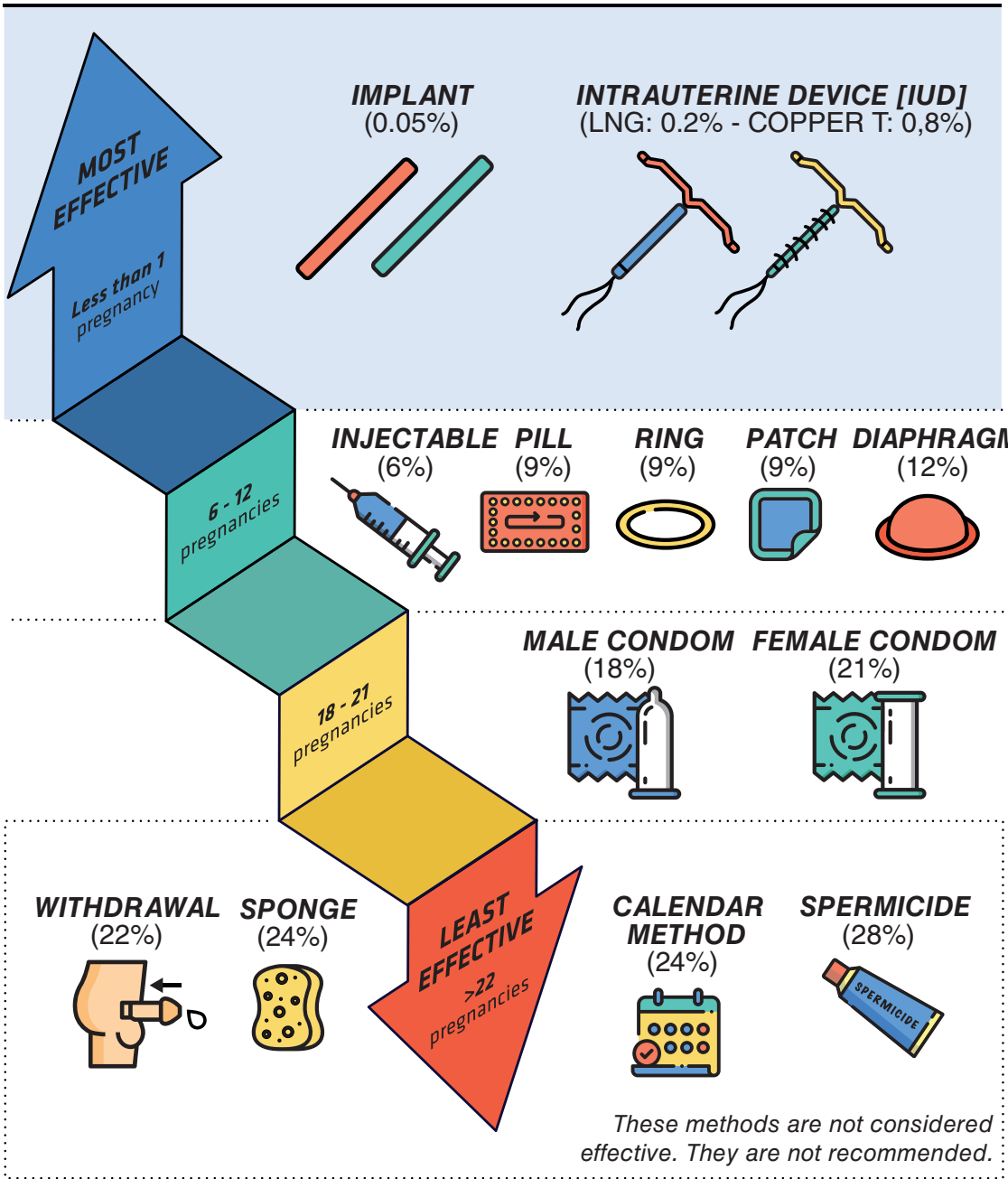

FIGURE 1 Effectiveness of family planning methods*

prior to planning a pregnancy.[18] Despite these recommendations, adolescents with diabetes are not aware of the risks of unplanned pregnancy and do not adequately prevent it and engage in risky behavior, with elevated levels of unprotected sex leading to unplanned pregnancy.[9,11,19,20] These data highlight the importance of education, counseling, and contraception for these adolescents and young women. The International Society of Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) recommend that education regarding pregnancy prevention begin during puberty, even before menarche.[18,21] However, the discussion of this

topic with adolescents with T1D is addressed unfrequently during regular clinic visits for the care of diabetes.[22]

The combination of education and contraception promotion reduces the risk of unintended pregnancies in healthy girls, and these results are likely to be applicable to girls with chronic conditions.[23] Therefore, the consideration of early counseling and the timely provision of highly effective contraceptives to adolescents with diabetes who are at risk of pregnancy is essential to prevent the personal, familial and social costs associated with unintended pregnancy in these teenagers.

This review is a state-of-the-art article on the use of LARCs in adolescents and young women with all types of diabetes.

2 | LARCs IN ADOLESCENTS

The recommendation to use LARCs as first-line contraception in adolescents is supported by the results of the "*Choice Project*", which provided reversible contraception at no cost.[24,25] This study enrolled 1404 adolescents aged 14 years to 19 years who received education about the contraceptive methods, including the different types of LARCs, combined oral contraception (COCs), depot medroxyprogesterone injections, rings and patches, and chose the method they preferred. The most frequently chosen methods were IUDs or implants (72%), followed by COCs (12%); subdermal progestin implants were the method most commonly selected by the adolescents (34.5%).[26] The cumulative unplanned pregnancy rate in the adolescents after a three-year follow-up was 0.9% for those who used LARCs and 9.4% for those who used non-LARC methods.[25] The continuation rate for LARCs was also higher than that for short-acting contraceptives at 24 months (77% and 44%, respectively).[26,27]

Despite all the advantages that may be associated with the use of LARCs by teenagers and young women, less than 5% of these women use one of these methods.[28] Adolescents continue to use short-acting methods, which have low effectiveness and a high discontinuation rate, as their first choice (Table 1). The low rate of use of LARCs in adolescents is related to barriers to their use, including difficulties gaining access to insertion, medical resistance, and the cost of the methods.[29] A trained professional must insert an IUD or implant. For patients with diabetes, the need for referral to a specialist may be an opportunity for timely counseling and the prevention of sexually transmitted disease.

The high initial cost of LARC implantation represents a critical barrier for patients who are not covered by insurance.[30] Payment or reimbursement for LARCs is required at the time of insertion and is due in a single payment, which is costly and thus may limit access for many young patients who do not have insurance for this type of contraception. However, when the duration of the effectiveness of a single LARC is considered, LARCs cost less than COCs (Table 2). Cost-effectiveness analyses of the use of LARCs must also address the costs of unintended pregnancy and related abortions. Therefore, when the high levels of adherence and long-term effectiveness associated with LARC use are taken into account, the annual expenses are lower than those of short-term methods.[31]

TABLE 2 Types and costs of different long-acting reversible contraceptive methods

Type of contraception	Hormone (dose)	Commercial name	Progestin daily release (μg/day)	Duration (years)	Annual costs USA (USD/year)*	Annual costs Chile (USD/year)**	Efficacy typical use (%)
Intrauterine device with levonorgestrel							
	Levonorgestrel (13.5 mg)	Skyla Jaydess	14	3	264	90	0.20
	Levonorgestrel (19.5 mg)	Kyleena	20	5	190	53	0.20
	Levonorgestrel (52 mg)	Mirena	19.5	5	190	53	0.20
Nonhormonal IUD							
	Copper intrauterine device (copper T380A)		0	10	6.1-7.8	2.0	0.80
	Multiload (250, 375)		0	5	19-21.6	6.4	0.7
	Intrauterine ball (copper SCu300A, B, C)	Ballerine®	0	5	NA	NA	1.4
Progestin implants							
	Etonogestrel (68 mg)	Implanon / Implanon NTX	60-70	3	208	56.1	0.05
	Levonorgestrel (75 mg)	Jadelle ®	75	5	NA	20.9	0.05
Combined oral contraceptives					300-480	30-338	
DMPA					150-308	225	

Note: * Data obtained from www.pharmacychecker.com; ** Data obtained from www.icmer.org and www.aprofa.cl.
Abbreviations: DMPA,Depot medroxyprogesterone acetate; IUD, intrauterine device; NA, cost not available.

3 | TYPES OF LARCS, TABLE 2)

LARCs include subcutaneous or IUDs, which in some cases contain progestins. The copper intrauterine device (Cu-IUD) is the only non-hormonal LARC. Progestin-containing IUDs and subcutaneous implants do not contain estrogens and are therefore a safe alternative for women with contraindications to estrogen use (eg, a history of migraine with aura or risk factors for thrombosis).[32]

4 | 1. - LONG-ACTING SUBDERMAL PROGESTIN IMPLANTS

Progestin implants are plastic devices that are placed in the subcutaneous tissue of the arm. The main reason women choose an implant is the desire to use a LARC method but not an intrauterine device. Two types of subdermal implants are commercially available (Table 2); they contain either etonogestrel (one rod) or levonorgestrel (two rods) and provide contraceptive protection for 3 years and 5 years, respectively. Implant insertion is an ambulatory procedure performed in an office by trained personnel. Both implants have been approved for use in nulliparous or multiparous women of any age.

The high contraceptive efficiency of the subdermal implants is achieved by increasing the viscosity of the cervical mucus, reducing the amount of cervical mucus, and inhibiting sperm penetration into the uterine cavity. However, the suppression of ovulation and alterations in the endometrium may also occur.[33]

The main side effect reported with the use of the implants is irregular bleeding, which is explained by the impact of progestin on the endometrium. Over time, most women experience a decrease in menstrual flow with an infrequent bleeding pattern. Amenorrhea may be observed in 25% to 35% of users. Most women consider the diminished frequency and quantity of menstrual flow a positive effect of the implant. Prolonged bleeding, however, is observed in one-fifth of the subjects and may lead to early extraction of the implant.[34,35] Mild weight gain and mood changes have also been reported in a minority of women.[36-38]

5 | INTRAUTERINE DEVICES

5.1 | COPPER-IUDs

Three types of Cu-IUDs are currently available: copper T-shaped IUDs, multiload IUDs, and the newer intrauterine balls (IUBs). These are non-hormonal methods and are preferred by women who want to avoid hormonal contraception and wish to have menstrual cycles but still seek a highly efficient contraceptive method (Table 2). The three types of Cu-IUDs have a frequency of unintended pregnancy lower than 1% per 100 women per year.

The most frequently used IUD is the copper T 380 A (T-Cu 380A), which is a T-shaped device. The multiload IUD is a horseshoe-shaped device, and the IUB is a Cu-IUD that, upon insertion into the uterus, takes a spherical shape.

All Cu-IUDs induce an inflammatory reaction secondary to the release of copper into the uterine cavity, which explains their contraceptive effect. Copper ions, prostaglandins, and macrophages reach high concentrations in intrauterine fluids and throughout the genital tract, creating a medium that is toxic to sperm and oocytes, impairing sperm motility, capacitation, and survival and reducing oocyte fertilization.[39-45]

The most common side effects of the T-shaped Cu-IUD are heavy menstrual bleeding and dysmenorrhea, which have been reported in 5% of users and may lead to discontinuation of use.[46] These symptoms have been postulated to be secondary to the inflammatory reaction of the uterus. Serious adverse effects are infrequent and include infection, uterine perforation, and pregnancy complications. Fertility returns immediately after the removal of the device.

5.2 | LEVONORGESTREL-RELEASING-IUDs

LNG-IUDs are T-shaped IUDs that are made of a polyethylene frame and contain different amounts of LNG. These types of LARCs have been approved by the Food and Drug Administration (FDA) and by the European Medical Agency (EMA) for use for 3 years to 5 years (Table 2). The main advantages of LNG-IUDs over other LARCs are the lighter menstrual periods with little systemic hormonal exposure.

LNG-IUDs induce the thickening of cervical mucus, the suppression of endometrial proliferation, and the impairment of sperm penetration into the uterine cavity, all mechanisms that are involved in the high contraceptive efficiency of this method. Some of the progestin that is contained in the LNG-IUD may be absorbed systemically, resulting in serum levels of LNG that can reach ~300 pg/mL, which is significantly lower than the 30 pg/ml serum levels observed with the subdermal progestin implant. Half of all users may exhibit diminished ovulation rates.[33]

Irregular menstrual bleeding, as a consequence of endometrial atrophy, is frequently observed during the first 3 months to 6 months of use. The amenorrhea rate increases with longer duration of LNG-IUD use, with 15.4% of users reporting amenorrhea at 12 months.[25] LNG-IUDs that contain higher doses of LNG are associated with a higher prevalence of amenorrhea at 1 year of follow-up; amenorrhea was observed in 25% and 10% of users of the 52 mg and the 13.5 mg LNG-IUDs, respectively. Similarly, functional ovarian cysts of up to 3 cc to4 cc in volume are more frequently observed with LNG-IUDs containing more progestin.

Other frequent complaints reported with the use of LNG-IUDs are acne in 25% of users and headache and mood changes in 14% and 11% of the users, respectively.[47]

6 | MYTHS AND PREFERENCES ABOUT IUDS AND SUBCUTANEOUS PROGESTIN IMPLANTS IN ADOLESCENTS

IUDs are not frequently recommended by OBGYNs for nulliparous women or adolescents. This reluctance to recommend IUDs for young

women has a historical basis. Health professionals have misconceptions that IUDs may have a high risk of uterine complications that are associated with problems with the future fertility of nulliparous women.[48] In part, these ideas arose from the fact that the first IUDs, known as the Lippes (1962) and Dalkon Shield (1971) systems, were made of inert materials that were associated with severe infections and toxic shock and, therefore, were discontinued in the late 1970s. Later, in 1988, the FDA approved the Cu-IUD for contraception use for up to 10 years.[49]

Another reason for the reluctance to recommend IUDs for young women has been the risk of lower genital tract and pelvic infections. This risk is higher the first month after insertion. Other factors that increase the risk of pelvic infections in both IUD users and non-users, are the number of sexual partners of the woman and her partner(s), the prevalence of STDs in the community and the age of the woman.[50] Therefore, the prevention of pelvic infections after IUD insertion should highlight the need to rigorously maintain an aseptic condition during the insertion of the IUD, rule out gynecological infections, and advice patients on the prevention of sexually transmitted infections.

7 | LARCS IN ADOLESCENTS WITH DIABETES

LARCs represent a good choice for patients with diabetes who already have a high burden of self-care related to their medical condition. However, this recommendation arises from expert opinion and consensus,[18,21] and there is a lack of studies evaluating the use of LARCs in adolescents with diabetes. The studies that have assessed the metabolic impact of these medications have evaluated adult women with diabetes, and they are reviewed in the following paragraphs.

Several factors must be considered in the selection of a contraceptive method in women with diabetes, including the duration of diabetes, the effect of the method on metabolic control, the presence of chronic complications, obesity, compliance, acceptability, and contraceptive efficiency. The estrogen contained in many types of hormonal contraceptive methods has a prothrombotic effect and is not recommended for women who have had any type of diabetes for longer than 20 years or for those who have micro- and macrovascular complications (Table 3). For these patients, non-hormonal IUDs may be used under any circumstance (category 1), and LND-IUDs or progestin implants may also be recommended (category 2).[51,52]

The selection of contraceptive methods for obese women with T2D requires special consideration. Theoretically, patients with T1D and T2D have similar eligibility criteria (Table 3). However, since most young women with T2D are obese, they have an elevated risk of thromboembolic events.[52] Obese women per se have an increased risk of deep venous thrombosis, but this risk increases as BMI increases.[53] Thus, COCs with estrogens are not recommended for women with BMI greater than 35 mg/kg, and LARCs are a safer option (Table 3). O'Brien et al. assessed the risk of thromboembolic events in women with T1D and T2D and concluded that IUDs and subdermal contraceptives are less likely than COCs to be associated with thromboembolism.[54] The avoidance of estrogen-containing contraceptives is even more critical when the patient has several risk factors for cardiovascular disease.

Weight gain may be a side effect of progestin-containing LARCs and has been reported in 5% to 22% of users.[55] A report from the "*Choice Project*"[56] that compared weight gain during the 1 year of use of three progestin-only contraceptive methods showed a weight gain of 2.1 kg for progestin implant users, 1.0 kg for LNG-IUD users and 0.2 kg for Cu-IUD users. The range of weight gain, however, was broad.[56] Bahamondes et al. reported a weight gain of 3 kg after 3 years of use of progestin-containing LARCs compared to a weight gain of 1 kg with Cu-IUD use.[57] Similar results have been reported in adolescents[37] and confirmed in a systematic review.[55] A Cochrane report did not observe significant weight gain in women with diabetes using progestin-only methods; however, the number of included studies was small.[58]

TABLE 3 Medical eligibility criteria for contraceptive use in patients with diabetes, cardiovascular risk factors and obesity

	Barrier	Combined contraceptives				Progestin only			IUD	
	Condom	Oral	Inject.	Patch	Vaginal ring	Oral	Inject.	Implant	Copper	Levonorgestrel
Diabetes										
No micro or macrovascular disease	1	2	2	2	2	2	2	2	1	2
Diabetes duration >20 year's duration	1	3/4	3/4	3/4	3/4	2	2	2	1	2
Microvascular complications	1	3/4	3/4	3/4	3/4	2	3	2	1	2
Macrovascular complications	1	3/4	3/4	3/4	3/4	2	3	2	1	2
Obesity	1	2	2	2	2	1	1	1	1	1
Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension)	1	3/4	3/4	3/4	3/4	2	3	2	1	2

Note: Adapted from: WHO., Fifth edition. 2015.[52] Recommendation category: 1. Use method under any circumstances; 2. Generally use the method; 3. Use of method not usually recommended unless other more appropriate methods are not available or not acceptable; 4. Method not to be used.
Abbreviation: IUD, intrauterine device.

Metabolic control is an essential element to consider when determining the best contraceptive option for women with diabetes. It is necessary to consider how the method may affect metabolic control; additionally, baseline metabolic control must be considered as well as how a person with diabetes, who must already contend with a large number of self-care tasks, might adhere to the contraceptive. Patients with poorly controlled diabetes, those who do not adhere to diabetes treatment, and those with low attendance at the diabetes clinic may represent a group of patients who will have problems with compliance with the daily use of COCs and may be at risk of unplanned pregnancy and significant hyperglycemia.

The effect of subdermal progestin implants on the metabolic control of diabetes was evaluated in two studies. The first study followed adult women (N:20) with T1D or T2D who used a levonorgestrel implant (38 mg) for 9 months.[59] No changes in metabolic control, insulin dose, or weight were found, but the women did show a decrease in HDL and LDL cholesterol with the use of this method.[59] The second study was published in 2008 by Vicente et al, who studied 23 women aged 12 years to 37 years with insulin-treated diabetes who used a progestin implant (Implanon) for 24 months.[60] The most common side effects were amenorrhea and infrequent bleeding, but no effects on BMI, daily insulin dose, or HbA1c levels was observed. No effect on microvascular complications was observed; however, a decrease in albuminuria was reported. Similar to the study by Diab et al, significant reductions in serum cholesterol, triglyceride, and HDL cholesterol levels were observed.

The effect of hormonal IUDs on glycemic control has been studied in adult women with T1D and T2D. Lang et al evaluated adult women with T2D using LNG-IUDs (n: 112) and showed a mild decrease in HbA1c and no effect on chronic microvascular complications or weight.[44] Rogovskaya evaluated women (N: 62) aged 18 to 45 years with T1D and without evidence of retinopathy or nephropathy who were randomized to receive LNG-IUD or TCU-380A with 12 months of follow-up. Both contraceptive methods had no significant effect on HbA1c levels or daily insulin requirements, and differences between the two groups were not reported.[61] Similarly, several other studies that have evaluated LNG-IUDs in women with T1D and T2D have shown no effect of LNG-IUDs or non-hormonal IUDs on metabolic control, total daily insulin dose, and lipid profile[42,55,56,44,59,61-66] However, no study has reported an in-depth evaluation of the glycemic profile using a continuous glucose monitoring system.

Similar to data published in non-diabetic women, the main benefit of LNG-IUDs is a less problematic menstrual flow than with non-hormonal Cu-IUDs.[61] Furthermore, the menstrual flow decreases over time with LNG-IUDs.[61] The rates of LNG-IUD expulsion and pelvic inflammatory disease reported in this series were 3.7% and 1.7%, respectively, with no cases of unintended pregnancy.[44] These data are similar to what has been reported for non-diabetic women.[67]

Some decades ago, IUDs were not a recommended contraceptive alternative for women with diabetes due to the fear of an increased infection rate in these patients. Recently, Goldstuck and Styne performed a systematic review of IUD use in women with T1D and T2D. Seven studies fulfilled the criteria for inclusion in this review. This systematic review concluded that copper IUDs and levonorgestrel-containing IUDs were suitable for women with diabetes without an increased risk of expulsion or infection.[63] Other studies have also shown that the pregnancy prevention rate in women with diabetes using Cu-IUDs was similar to that in the general population.[68,69]

In conclusion, the prevention of adolescent pregnancy continues to be a significant public health concern, and pregnancy prevention is of even greater importance in adolescents with diabetes, in whom poor metabolic control can lead to very high-risk pregnancies. Short-acting oral contraception has an unacceptably high rate of failure and unplanned pregnancy in adolescents; in young women with diabetes, unplanned pregnancy may have long-term consequences for the child's health. LARCs are an efficient method for pregnancy prevention that is not user dependent and has a positive safety profile in women with diabetes. Therefore, consistent with the recommendations from the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, LARCs should be considered a first line choice for contraception in adolescents and young women with T1D and T2D. Unfortunately, the indications and use of these methods have been primarily studied in adult women with diabetes. Future well-designed studies that determine in-depth the glycemic changes associated with LARCs use in young women with diabetes are greatly needed.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

PEER REVIEW

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