Reproductive-age women with diabetes mellitus are in one of two categories: those desiring pregnancy or those not desiring pregnancy. For women who desire pregnancy, referral to an obstetrician/gynecologist for preconception counseling is essential, and excellent preconception glycemic control is necessary to decrease the risk of congenital anomalies and fetal loss. For women wishing to postpone pregnancy, a comprehensive contraceptive plan is imperative.
There is a growing need for careful contraceptive counseling in women with diabetes mellitus. From 1990 to 1998, rates of diabetes mellitus increased 70% in women aged 30 to 39 years. As Figure 1 indicates, an increasing number of Americans are being diagnosed with diabetes mellitus compared with two decades ago. Currently, 1.85 million women of reproductive age (ie, 18 years to 44 years) have diabetes mellitus, and an estimated 500,000 women of this age have undiagnosed diabetes. The comorbidities associated with diabetes mellitus, such as cardiovascular disease, renal impairment, retinopathy and morbid obesity, are becoming more common in women of reproductive age. Therefore, a contraceptive plan is essential for women with diabetes mellitus who are at risk for pregnancy, and counseling of these women must take into account the relative safety of most forms of contraception, as well as the risks associated with pregnancy. Contraceptive counseling for women with diabetes mellitus must be evidence-based and combined with education materials that emphasize current safety data for hormonal contraceptive choices as they apply to such patients. The present evidence-based review of contraceptive use in women with diabetes mellitus includes safety data and key counseling points to assist clinicians in providing appropriate contraceptive choices for this patient population. Using guidelines in “U.S. Medical Eligibility Criteria for Contraceptive Use, 2010” (See Figure 2), published by the Centers for Disease Control and Prevention (CDC), the present article explains and outlines current recommendations, taking into account patient risk factors and comorbidities.

Contraceptive risks
Women with diabetes mellitus need evidence-based contraceptive counseling, but many clinicians may focus on the risks of hormonal contraceptives while neglecting the potential risks of unintended pregnancy in these patients. Although text included in hormonal contraceptive package inserts and patient education resources lists risks related to the products, some of this text is the result of class labeling or legal concerns rather than evidence-based medicine. It is important to keep in mind that women with diabetes mellitus are at significantly higher risk of pregnancy complications than are women without diabetes, and the actual health risks of pregnancy often overshadow the risks of hormonal contraception. To make the best decisions based on each patient’s unique medical problems and lifestyle, it is crucial to understand which of the listed “risks” are evidence-based.

Pregnant women with diabetes mellitus are considered at high risk because of the increased maternal morbidity and mortality associated with pregnancy. These risks include preeclampsia and new onset of diabetes-related morbidities, such as nephropathy, retinopathy and worsening of preexisting vascular or renal disease. The risks of such maternal complications are greater in patients with long-standing or poorly controlled diabetes mellitus than in other women.

Pregnancy-related complications also occur more often in women with diabetes mellitus than in women without diabetes. These complications include higher rates of spontaneous miscarriage, polyhydramnios, pregnancy-induced hypertension, cephalopelvic disproportion and cesarean section. When the risks of pregnancy are compared to the risks of each contraceptive option, it becomes clear that there are many safe and effective contraceptive choices for women with diabetes mellitus—even those women who have moderately advanced disease.

With regard to fetal or neonatal morbidity and mortality, physicians should be aware that congenital anomalies are eight times more likely in patients with diabetes mellitus (rate of 5.1%–9.8%) than in patients without diabetes. Such anomalies often involve the cardiovascular, renal, skeletal, and central nervous systems. Because organogenesis occurs during weeks three to six of gestation, rates of congenital anomalies in women with diabetes who had strict pre-pregnancy glycemic control have been similar to rates in normoglycemic controls. Other congenital complications associated with diabetes mellitus include macrosomia, respiratory distress syndrome and neonatal hypoglycemia.

Overview of contraceptive choices
When considering contraceptive options for women with diabetes mellitus, assessing both efficacy and safety is important. Efficacy is highest for long-term contraceptive methods, somewhat less high for short-term hormonal therapies (for which daily, weekly, monthly or quarterly dosing may affect adherence and, thus, efficacy), and lowest for barrier or behavioral methods. The three long-term contraceptives available in the United States are the 10-year Copper T 380A (ParaGard®; Duramed Pharmaceuticals Inc, Cincinnati, Ohio) intrauterine device (IUD), the five-year levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena®; Bayer HealthCare Pharmaceuticals Inc, Wayne, New Jersey), and the three-year etonogestrel-releasing subdermal implant (Implanon®; Merck & Co Inc, Whitehouse Station, New Jersey). Short-term methods involving estrogen-and-progestin combinations include...
Long-term methods

Contraceptives that do not rely on active participation of the patient have the highest efficacy among contraceptive methods, as well as very high safety ratings for patients with diabetes mellitus, regardless of severity of disease. The Copper T 380A, the LNG-IUS and the subdermal implant offer three excellent choices for patients. Although long-term methods are considered last by many patients and clinicians, the efficacy and safety of these methods warrant their consideration as first-line defense against unintended pregnancy. All three devices are easily placed by a physician or midlevel provider in an office setting. Placement takes just a few minutes and provides long-term reversible contraception with rapid return to baseline fertility after removal.

Intrauterine contraception

The Copper T 380A and the LNG-IUS are the two IUDs available in the United States. Despite high efficacy, safety and convenience, intrauterine contraception is underutilized in the United States, with only 5.5% of U.S. women using these devices. The Copper T 380A does not contain hormones, while the LNG-IUS does. Thus, these devices have different adverse-effect profiles, expected bleeding patterns and benefits to patients.

The duration of action of the Copper T 380A is listed as 10 years. Instead of releasing hormones, this device provides contraceptive efficacy secondary to the effect of copper ions in the uterine environment. It impairs sperm motility, alters the composition of cervical mucus and prevents fertilization.

Safe in nulliparous and parous women alike, the Copper T 380A is rated by the CDC as safety category 1 (1=most safe to 4=least safe) for all patients with diabetes mellitus, regardless of severity of disease. Because this IUD can increase menstrual flow and lengthen duration of bleeding, caution is advised for women who have bleeding-related problems, such as heavy periods, anemia, fibroids or anticoagulation.

With few contraindications, this method of contraception is safe, effective and easily placed in the office setting. Women who are sensitive to progestin-related adverse effects and who have normal menstrual patterns are typically excellent candidates for the Copper T 380A.

The hormone-releasing LNG-IUS is also an excellent contraceptive choice for most women with diabetes mellitus, regardless of the severity of their diabetes or related comorbidities. With a CDC safety classification of category 2—meaning the advantages of using this contraceptive generally outweigh the theoretical or proven risks—the LNG-IUS may be considered for almost any patient. Besides having a high safety rating, it also has high efficacy and patient satisfaction. It prevents pregnancy by impairing sperm motility and thickening cervical mucus.

With high intrauterine levels, but relatively low systemic levels of levonorgestrel, the LNG-IUS provides a dramatic reduction in menstrual blood loss with relatively few hormone-related adverse effects. This device has indications not only for contraception,
The etonogestrel-releasing implant is safe (C D C safety category 2) for women with diabetes mellitus, and it provides the highest efficacy of any reversible contraceptive. 20 This 4-cm subdermal implant releases etonogestrel, a progestin, to prevent pregnancy for as long as three years. 21 With low systemic levels of progestin, contraceptive efficacy is achieved through two mechanisms: ovulation inhibition and thickening of the cervical mucus.

In a study of metabolic effects of the subdermal implant in women with diabetes mellitus, there was a statistically significant reduction of total serum cholesterol, no change in low-density lipoprotein cholesterol (LDL-C) level, and no change in the ratio of high-density lipoprotein cholesterol (HDL-C) to total cholesterol. 22 Carbohydrate metabolism was unchanged over the two-year study period, and no aggravation of vascular lesions was noted.

### Subdermal implant

The etonogestrel-releasing implant is safe (CDC safety category 2) for women with diabetes mellitus, and it provides the highest efficacy of any reversible contraceptive. 20 This 4-cm subdermal implant releases etonogestrel, a progestin, to prevent pregnancy for as long as three years. 21 With low systemic levels of progestin, contraceptive efficacy is achieved through two mechanisms: ovulation inhibition and thickening of the cervical mucus.

### Guidelines from the U.S. Centers for Disease Control and Prevention (CDC) for assessing contraceptive safety based on individual patient scenarios.

<table>
<thead>
<tr>
<th>Severity of disease</th>
<th>Combined hormonal (pill, patch, ring)</th>
<th>Progestin-only pill</th>
<th>Injection (DMPA)</th>
<th>Implant (Implanon®)</th>
<th>LNG IUS (Mirena®)</th>
<th>Copper T 380A (ParaGard®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus without vascular disease*</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus with vascular disease* OR Duration &gt;20 years</td>
<td>3/4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Nephropathy, neuropathy, retinopathy or other vascular disease.

**Abbreviations:** DMPA—depot medroxyprogesterone acetate; LNG-IUS—levonorgestrel-releasing intrauterine system.

With appropriate patient selection, continuation rates of implant use are high. Bleeding irregularity is the main reason for discontinuation in U.S. women. Minimal weight gain is another. Bleving irregularity is the main reason for discontinuation in some women. The ideal patient for the subdermal implant would be a woman who desires the highest contraceptive efficacy and a simple method of insertion and who would be tolerant of irregular bleeding patterns.

**Estrogen-and-progestin combination pills and other methods**

The most widely prescribed forms of contraception in the United States are those containing both estrogen and progestin. These hormonal therapies include oral contraceptive pills, vaginal rings and patches. Combination therapies contain a range of ethinyl estradiol doses and varying types of progestins, which prevent pregnancy by blocking the luteinizing hormone surge (which would otherwise trigger ovulation) and by thickening cervical mucus.

All combination contraceptives have similar efficacy and continuity data, with a 0.3% failure rate with perfect use in the first year and an 8.7% failure rate with typical use in the first year. However, only approximately 66% of patients continue combination contraceptive use one year after starting the therapy. Because pills must be taken daily, patches must be changed weekly, and rings must be changed monthly, a patient’s ability to adhere to each regimen must be carefully assessed.

Estrogen-containing contraceptives are preferred by many women because these methods offer such noncontraceptive benefits as improvement in acne, reduction in dysmenorrhea, decreased menstrual flow, and suppression of ovarian cysts. For women with diabetes mellitus who have no subsequent vascular disease, the advantages of combination contraceptive methods generally outweigh any theoretical or proven risks associated with these options. However, because estrogen increases the risk of clotting, caution must be used when prescribing combination contraceptive methods for women with diabetes in whom vascular co-morbidities have developed.

In patients who have evidence of end-organ damage or who have had diabetes mellitus for more than 20 years, combination therapy is usually not recommended unless other contraceptive options are not available or acceptable. Figure 2 shows CDC guidelines for assessing contraceptive safety based on individual patient scenarios.

As with any clinical decision, both clinical guidelines and individualized risk stratification must be considered when initiating a new contraceptive. Because diabetes mellitus is often diagnosed in the context of metabolic syndrome, it is important to consider the effects of combination estrogen-and-progestin therapy on both carbohydrate and lipid metabolism. However, with careful monitoring and appropriate counseling of patients, physicians should feel confident in prescribing combination therapy to women with diabetes mellitus. Studies of women with type 1 diabetes mellitus (T1DM) who used oral contraceptives have shown no change in levels of glycosylated hemoglobin or degree of nephropathy and retinopathy, compared to women with T1DM who did not use oral contraceptives. These findings suggest that these medications did not accelerate vascular disease in the patients.

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**Discussing diabetes, pregnancy and birth control with women**

**Birth control options for women with diabetes**

Choosing a safe and effective birth control method can be particularly confusing when patients are concerned about risks related to diabetes control.

Following are some questions to review with your patients before making a decision about birth control:

1. How long until you want to become pregnant?
   - Months, one year, five or more years?
2. What birth control methods have you used in the past?
   - What were the pros and cons?
3. How frequently do you want to take or change your birth control?
4. Do you have any other risk factors that would limit your options? For example:
   - smoking and over age 35
   - history of heart attack, stroke or blood clots
   - migraine with visual changes
   - uncontrolled high blood pressure
   - liver or gallbladder diseases

**Some birth control options for patients to consider:**

- Combined Hormonal:
  - oral contraceptive pills
  - Ortho-Evra™, patch
  - NuvaRing®, vaginal ring
  - Three-year implant (Implanon®)

- Intrauterine Device (IUD):
  - Mirena®, progesterone only
  - Copper T 380A, no hormones

- Barrier Methods:
  - Condoms/diaphragms

- Behavioral Methods
  - Natural Family Planning
  - Withdrawal

- Sterilization
  - Tubal ligation/Essure®/Adiana®
  - Vasectomy

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Elevations in lipid levels, including total cholesterol, HDL-C and triglycerides, have been noted in patients using oral contraceptives. In addition, oral contraceptives are associated with decreased insulin sensitivity. These metabolic effects seem to vary depending on the progestin component included in the pill. Levonorgestrel has been associated with decreased insulin sensitivity. However, pills containing drospirenone, desogestrel or gestodene tend to be metabolically neutral in terms of carbohydrate metabolism. Despite these trends in lipid alterations, it is still considered safe to use combination contraceptives in patients with lipid dysfunction in the absence of more severe comorbidities because the benefits of contraception outweigh the risks.

Once combination contraceptive therapy is determined to be a safe option for a patient with diabetes mellitus, the physician and patient must select which formulation is best—pills, vaginal rings or patches. This decision should be driven by both patient preference and patient lifestyle, with some consideration given to the potential metabolic effects based on route of administration.

**Intravaginal ring**

NuvaRing® is a vaginal ring containing etonorgestrel (an active form of desogestrel) as the progestin component, along with ethinyl estradiol. The steroid hormones in the ring are absorbed directly through the vaginal mucosa, minimizing first-pass metabolism through the liver and causing 30% to 40% less hormone exposure than from oral administration. The advantage of this local hormone administration is that fewer systemic effects have been noted in women with diabetes mellitus. Unlike use of oral contraceptives, use of the vaginal ring has resulted in no statistically significant change in total cholesterol or HDL-C levels—though a continued elevation in triglyceride levels has been noted with the ring.

The vaginal ring is an excellent contraceptive method for women with diabetes mellitus who have no vascular disease and who prefer monthly administration, the benefits of an estrogen-containing contraceptive and a method they can control themselves.

**Transdermal contraception**

Ortho Evra™ is a contraceptive skin patch that delivers 0.15 mg daily of norelgestromin and 20 mcg daily of ethinyl estradiol transdermally. With hormone exposure similar to doses found in 35 mcg combination pills, this method typically has such adverse effects as nausea and breast tenderness. The patch is changed once weekly for three weeks. It is then removed to allow for a one-week withdrawal bleed before placing the next patch.

One consideration of patch use for patients with diabetes mellitus is that in clinical trials, women weighing more than 90 kg had a greater failure rate than women with weight less than 90 kg. Concern regarding increased risk of thrombophilia is another consideration. One study showed the patch resulting in a more than two-fold increased relative risk of venous thromboembolism in patients without diabetes, compared to use of a 35 mcg norgestimate oral contraceptive. This risk was lower than the risk of venous thromboembolism associated with pregnancy.

The contraceptive patch is appropriate for women with diabetes mellitus who have no vascular disease and who have a normal body mass index and a strong desire for the benefits of an estrogen-containing contraceptive via weekly transdermal administration.

When making recommendations regarding estrogen-containing contraceptives, it should be kept in mind that the American Congress of Obstetricians and Gynecologists guidelines for contraceptive use emphasize that the following risk factors outweigh the benefits of combination therapies: smoking and age greater than 35 years; uncontrolled hypertension; personal history of stroke; ischemic heart disease or venous thromboembolism; migraine with aura; and current breast cancer or history of breast cancer with active disease within the previous five years.

**Progestin-only methods**

Depot medroxyprogesterone acetate (DMPA) is an injectable progestin-only contraceptive that is administered every three months by intramuscular injection. Although highly effective in preventing pregnancy, DMPA has adversely affected carbohydrate and lipid metabolism.

Use of DMPA causes only minimal changes in glucose tolerance, but its effects on lipid metabolism include increases in LDL-C and decreases in HDL-C. Because of the adverse lipid effects of DMPA, this form of contraception has a CDC safety rating of category 3, meaning that risks outweigh benefits in individuals with vascular disease or other longstanding illness.

**Progestin-only pills**

According to CDC guidelines, progestin-only pills (Micronor® [norethindrone]; Ortho-McNeil-Janssen Pharmaceuticals Inc, Raritan, New Jersey) have a safety classification of category 2 for all patients with diabetes mellitus—with or without vascular disease. This safety rating makes the pills an appropriate choice for individuals who have diabetes with hypertension or vascular disease. Because this contraceptive method does not interfere with lactation, it is often chosen for breastfeeding women during the immediate postpartum period.

While progestin-only pills are safe, adherence with this contraceptive option requires consistent daily dosing, and nonadherence results in significantly decreased efficacy.

**Emergency contraceptive options**

Safe to use for patients with diabetes mellitus, emergency contraceptive options (Plan B One-Step™ [Teva Women’s Health Inc, Woodcliff Lake, NJ])...
Barrier methods and natural family planning

Condoms with spermicide, diaphragms, and natural family planning can be effective contraceptive methods when used consistently and correctly. However, these methods typically have the highest failure rates because they are user-dependent, with efficacy rates depending on patient adherence to recommended use. These methods may be considered for women who have spiritual beliefs that preclude the use of other methods of contraception, for women planning pregnancy within the next six months, or rarely-for women with contraindications to every other method.

Women choosing these methods should be informed about emergency contraceptive methods. For those women who desire a highly effective contraceptive without hormones, the Copper T 380A, previously discussed, is the best method. 30

Sterilization

For women who have completed childbearing or who are confident that they will never desire pregnancy, surgical sterilization is an excellent option. However, sterilization procedures do not offer any of the noncontraceptive benefits of some of the hormonal methods previously outlined.

A woman may choose from three methods of surgical sterilization: minimally invasive tubal occlusion (Essure® [Conception Inc, Mountain View, California] or Adiana® [Hologic Inc, Bedford, Massachusetts]); laparoscopic tubal ligation (clips, rings, or cautery); or tubal ligation at the time of cesarean section or other laparotomy. Efficacy is high for all three sterilization procedures, with the minimally invasive options of tubal occlusion offering the benefits of fast recovery time, minimal surgical risk, and exceptionally high efficacy rates.

Vasectomy for the male partner is a surgical sterilization option for any couple in a life-long relationship. Of course, vasectomy has the drawback of providing no individual contraception for the woman should she have a change of partner.

Final notes

Contraceptive counseling is essential for women with diabetes mellitus. Yet, these patients are less likely to receive such counseling than are women without diabetes, 40 because physicians are often focused on the management of the diabetes. Physicians need to address contraceptive choices with their patients who have diabetes mellitus, because use of an appropriate contraceptive results in lower risks of morbidity and mortality compared with the risks of pregnancy.

The safety guidelines established by the CDC can help physicians feel confident about their ability to provide safe contraceptive choices for women with diabetes mellitus, even those patients who have advanced disease. Patients with diabetes mellitus should be counseled about all contraceptive options, including such long-term methods as IUDs and subdermal implants as first-line recommendations.

References


