



## Contraceptive options for women with metabolic syndrome

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*Metabolic syndrome* is a term used to describe the common sequelae found in the context of obesity and includes hypertension, hypertriglyceridemia, dyslipidemia, and impaired glucose regulation, which lead to increased cardiovascular and metabolic risks. In women with metabolic syndrome, pregnancy planning is an important part of providing comprehensive health care. Therefore, clinicians must be aware of the safety and effectiveness of contraceptive options in this population. Guidelines presented by the Centers for Disease Control and Prevention in June 2010 listed the criteria for medical eligibility for current contraceptive options. Because of the growing rate of obesity, many recent studies have focused on assessing contraceptive safety and effectiveness specifically in these patients. Depending on the severity of each patient's disease, these guidelines can assist clinicians in presenting an evidence-based review of the safest and most effective options while recognizing the risks and benefits of each. When considering contraceptive options, it is important to compare not only the risks of contraception methods themselves but also to the risks associated with pregnancy and the postpartum period. Many safe and effective options are available for patients, and some of the best choices are user-independent, long-acting methods.

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With both clinicians and patients becoming increasingly aware of the metabolic and cardiovascular risks associated with metabolic syndrome, choosing safe and effective contraception for these patients can be challenging. The associated medical problems of obesity—diabetes, hypertension, lipid abnormalities, and vascular disease—raise concerns regarding the potential risks of using hormonal contraception in patients with metabolic syndrome. Fear of exacerbating disease may prevent clinicians and patients from choosing effective hormonal options, leaving these women at risk for unintended pregnancy. However, effective contraception is essential for patients with metabolic

syndrome who do not desire pregnancy, because pregnancy significantly increases their risks of weight gain, thrombophilia, diabetes, hypertension, and other causes of morbidity and mortality. This evidence-based review of contraceptive use in women with metabolic syndrome presents safety and effectiveness data accompanied by key counseling points to assist clinicians in providing appropriate contraceptive choices for this patient population. Using the guidelines in *US Medical Eligibility Criteria for Contraceptive Use, 2010* (Table 1) published by the Centers for Disease Control and Prevention (CDC), this article explains and outlines current recommendations, taking into account patient risk factors and comorbidities.<sup>1</sup> Many safe and effective options are available for patients, and some of the best choices are user-independent, long-acting methods.

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**Table 1** US Medical Eligibility Criteria for Contraceptive Use, 2010

Condition	Qualifier for condition	Combined hormonal (pill, patch, ring)	Progestin-only pill	Injection (DMPA)	Implant Implanon	LNG-IUS Mirena	Copper T 380A Paraguard
Diabetes mellitus	DM without vascular disease	2	2	2	2	2	1
	DM with end-organ damage or >20 years duration	3/4	2	3	2	2	1
Hypertension	During pregnancy only—now resolved	2	1	1	1	1	1
	Well-controlled	3	1	2	1	1	1
	Systolic 140–159 mm Hg or Diastolic 90–99 mm Hg	3	1	2	1	1	1
	Systolic >160 mm Hg or Diastolic >100 mm Hg	4	2	3	2	2	1
Obesity	With vascular disease	4	2	3	2	2	1
	≥30 kg/m <sup>2</sup> BMI	2	1	1	1	1	1
	Menarche to <18 yrs and ≥30 kg/m <sup>2</sup> BMI	2	1	2	1	1	1
Hyperlipidemia		2/3	2	2	2	2	1

1 = No restriction for the use of the contraceptive method. 2 = Advantages of using the method generally outweigh the theoretical or proven risks. 3 = Theoretical or proven risks usually outweigh the advantages of using the method. 4 = Unacceptable health risk if the contraceptive method is used. Adapted from U.S. Medical Eligibility Criteria for Contraceptive Use, 2010.<sup>1</sup>

Obesity has reached epidemic proportions in the United States and around the world. From 2007 to 2008, the prevalence of obesity in adult women was 35.5%.<sup>2</sup> As the prevalence of obesity has increased in recent decades, the term *metabolic syndrome* has been defined and redefined to describe the clustering of metabolic abnormalities that occur in the context of obesity. Although different groups have defined metabolic syndrome differently, the International Diabetes Federation (IDF) met in 2005 to create a new worldwide definition that combined the input of several international health organizations (Table 2).<sup>3</sup> Central obesity with coexisting hyperlipidemia, hypertension, and impaired glucose regulation are the hallmarks of this syndrome.<sup>4-6</sup> Metabolic syndrome is also important in the context of the safety and effectiveness of contraception as physicians make recommendations to women with coexisting chronic medical diseases such as those found in metabolic syndrome. *Obesity* is defined as a body mass index (BMI) >30 kg/m<sup>2</sup> (Table 3). Limited studies have shown that obese women are at a similar risk for unintended pregnancy as are women of normal weight.<sup>7,8</sup>

In the United States, 49% (3.1 million) of all pregnancies per year are unintended, and approximately 0.5 million are associated with contraceptive failures.<sup>9</sup> In a recent survey of women with diabetes, 50% to 66% reported an unplanned

pregnancy.<sup>10</sup> Unfortunately, most contraceptive research has excluded women above 130% of ideal body weight, making it difficult to inform women regarding risk for contraceptive failure or the safety of each method.<sup>11</sup> Currently, no safety data exist regarding the use of contraception in women with a BMI >40 kg/m<sup>2</sup>.<sup>12</sup> Several studies have demonstrated that the increased adipose tissue found in women of higher weight and BMI may process the steroid hormones found in modern contraceptives differently than women of normal weight because of increased enzyme metabolism in the liver and higher steroid uptake into the adipose tissue itself.<sup>13,14</sup>

### Weighing contraceptive risks against the known risks of pregnancy

Fear of weight gain is likely a barrier to choosing hormonal contraception, because both patients and clinicians are concerned that contraceptive use will cause weight gain and exacerbate metabolic problems. However, several studies have failed to demonstrate a direct link between contraceptive use and weight gain. Combination hormonal contraception (including the pill, patch, and ring) has not been asso-

**Table 2** International Diabetes Federation (IDF) definition of metabolic syndrome<sup>3</sup>

Central obesity	Defined as waist circumference: Europids* ≥94 cm men ≥80 cm women South Asians ( <i>Based on a Chinese, Malay and Asian-Indian population</i> ) Male ≥90 cm Female ≥80 cm Chinese Male ≥90 cm Female ≥80 cm Japanese Male ≥85 cm Female ≥90 cm PLUS ANY TWO OF THE FOLLOWING:
Hyperinsulinemia	Type 2 diabetes Impaired fasting glucose (≥100 mg/dL [5.6 mmol/L]) Impaired glucose tolerance
Hypertension	Antihypertensive medication High blood pressure ≥130 mm Hg systolic ≥85 mm Hg diastolic
Elevated triglycerides	Current treatment for hypertriglyceridemia Plasma triglycerides (≥150 mg/dL [≥1.7 mmol/L])
Low HDL cholesterol	HDL cholesterol (<40 mg/dL (<1.03 mmol/L) in ♂ <50 mg/dL (1.29 mmol/L) in ♀)

\*Until further data can be collected, Ethnic South and Central Americans, Sub-Saharan Africans, Eastern Mediterranean, and Middle East (Arab) populations should use the Europid criteria.

ciated with significant weight changes.<sup>15,16</sup> Implanon, the etonogestrel subdermal implant, appeared in limited studies to have no associated weight gain.<sup>17,18</sup> A study by Hassan et al. demonstrated no weight gain in women using the copper intrauterine device (IUD) or barrier methods.<sup>19</sup> Several studies have reported a small weight increase in patients using the levonorgestrel-releasing IUD, but that that weight gain was no more than the baseline age-related weight gain over time.<sup>20,21</sup> Depot medroxyprogesterone acetate (DMPA) injection is the only contraceptive method in which weight gain, however controversial, has been reported. Some studies have shown DMPA to be weight neutral, whereas others showed a significant increase in weight, specifically in adolescents with preexisting obesity.<sup>22-24</sup>

Women with metabolic syndrome need evidence-based contraceptive counseling, but many clinicians may focus on the risks of hormonal contraceptives given these patients' multiple medical conditions, while neglecting the potential

risks of unintended pregnancy. Although information printed in hormonal contraceptive package inserts and patient education resources list risks related to the products, some of the implied risks are the result of class labeling or legal concerns rather than evidence-based medicine. It is important to keep in mind that women with metabolic syndrome are at significantly higher risk of pregnancy complications than are healthy women, and the actual health risks of pregnancy are often more significant than 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 obesity and metabolic syndrome are considered at "high risk" and they face increased risk of maternal morbidity and mortality compared with normal women. Pregnancy for women with obesity carries an increased risk of fetal congenital abnormalities including spina bifida and omphalocele.<sup>25</sup> Pregnancy-related morbidities are also higher in the obese population and includes increased rate of induction of labor, emergency cesarean section, gestational diabetes, pregnancy-induced hypertension, and preeclampsia.<sup>26-31</sup> The risks of such maternal complications are greater in patients with long-standing or poorly controlled disease than in other women. Preconception counseling and diabetes screening is recommended for women with metabolic syndrome. It is the standard of care to screen pregnant women with obesity or metabolic syndrome for diabetes in early pregnancy because they carry a higher risk of undiagnosed preexisting diabetes.<sup>32</sup>

The combination of diabetes mellitus and pregnancy substantially raises both fetal and maternal risks. Physicians should educate patients that not only is pregnancy loss more common, but also fetal anomalies are eight times more likely in pregnancies complicated by diabetes mellitus (rate of 5.1–9.8%) than in those without diabetes. Such anomalies often involve the cardiovascular, renal, skeletal, and central nervous systems.<sup>33,34</sup> Because organogenesis occurs during weeks 3 to 6 of gestation, rates of congenital anomalies in women with diabetes who had strict prepregnancy glycemic control have shown similar anomaly rates to nor-

**Table 3** Body mass index categories

Underweight	<18.5 kg/m <sup>2</sup>
Normal Weight	18.5–24.9 kg/m <sup>2</sup>
Overweight	25.0–29.9 kg/m <sup>2</sup>
Obese	
Class I Obesity:	30.0–34.9 kg/m <sup>2</sup>
Class II Obesity:	34.9–39.9 kg/m <sup>2</sup>
Very Obese (Class III Obesity, severe, extreme, morbid)	>40.0 kg/m <sup>2</sup>

Centers for Disease Control and Prevention and World Health Organization BMI Categories. Adapted from <http://www.euro.who.int/en/what-we-do/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi> and [http://www.cdc.gov/healthyweight/assessing/bmi/adult\\_bmi/index.html](http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html).

moglycemic controls, indicating that excellent preconception glycemic control can substantially decrease fetal risk.<sup>35,36</sup> Other complications associated with diabetes mellitus include macrosomia, respiratory distress syndrome, and neonatal hypoglycemia.<sup>36-38</sup> Maternal and fetal morbidity and mortality is substantially higher in diabetics, and these risks should be discussed with an obstetrician/gynecologist before conception.

## Overview of contraceptive choices

When considering contraceptive options for women with diseases that comprise metabolic syndrome, 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, OH) IUD, the five-year levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena; Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ), and the three-year etonogestrel-releasing subdermal implant (Implanon; Merck & Co Inc., Whitehouse Station, NJ). Short-term methods involving estrogen-and-progestin combinations include daily oral contraceptives, the monthly vaginal ring (NuvaRing; Merck & Co Inc.), and the weekly contraceptive patch (Ortho Evra; Ortho-McNeil-Janssen Pharmaceuticals Inc., Raritan, NJ). Short-term progestin-only methods include the quarterly DMPA injection (Depo-Provera; Pfizer Inc., New York, NY) and daily progestin oral contraceptives. Emergency contraception is another short-term hormonal option. Nonhormonal barrier and behavioral methods include male and female condoms, diaphragms, caps, shields, spermicides, the withdrawal method, fertility awareness, and natural family planning. Elective sterilization may be considered, for those who desire non-reversible contraception.

## Longer-term methods

Contraceptives that do not rely on active participation of the patient not only have the highest efficacy among contraceptive methods, but they also have very high safety ratings for women with metabolic syndrome, regardless of severity of disease. The Copper T 380A, the LNG-IUS, and the subdermal implant offer three excellent choices for these 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. IUD placement and subdermal implant insertion is easily accomplished in most patients with obesity; however, morbid obesity may make IUD placement slightly more challenging for the clinician and may require longer instruments to ensure proper placement. 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 underused in the United States, with only 5.5% of women using these devices.<sup>39</sup> The Copper T 380A does not contain hormones, whereas the LNG-IUS contains the progestin levonorgestrel. Thus, these devices have different adverse-effect profiles, expected bleeding patterns, and benefits to patients.

Safe in nulliparous and parous women alike,<sup>40</sup> the Copper T 380A is rated by the CDC as safety category 1 (1 = most safe to 4 = least safe) for all patients with metabolic syndrome, regardless of severity of disease. 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.<sup>41</sup> 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 ongoing 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 metabolic syndrome regardless of severity of disease. With a CDC safety classification of category 1 or 2 in the context of metabolic syndrome, the advantages of using this contraceptive generally outweigh the theoretical or proven risks. Therefore, the LNG-IUS may be considered for almost any patient with metabolic syndrome. In addition to a high safety rating, it also has high efficacy and excellent patient satisfaction. It prevents pregnancy by impairing sperm motility and thickening cervical mucus.<sup>41</sup>

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 or alterations in metabolic homeostasis.<sup>21,42</sup> This device not only has indications for contraception, but also for the treatment of heavy menstrual bleeding. In obese women, this therapy not only provides protection from pregnancy but may also prevent endome-

trial hyperplasia and uterine cancer, both of which are more common with obesity.<sup>43-49</sup> The LNG-IUS does not change metabolic parameters. Failure rate was similar in both obese and normal-weight controls.<sup>44</sup> A study comparing the LNG-IUS with the Copper T 380A in women with diabetes showed no differences in daily insulin requirement, glycosylated hemoglobin levels, or fasting blood sugar levels after 12 months of use.<sup>50</sup>

Despite the benefits and efficacy of the LNG-IUS and Copper T 380A, these devices are underused in the United States because of several reasons. Many patients and clinicians are concerned that these devices may not be safe for teenagers or for nulliparous women. Data from previous decades suggesting higher rates of pelvic inflammatory disease with the use of older types of IUDs are not easily forgotten. To the contrary, there are several recent studies documenting both the safety and efficacy of the LNG-IUS and Copper T 380A in teenagers and nulliparous women.<sup>40,51,52</sup>

The physician should be prepared to discuss evidence-based safety recommendations regarding the LNG-IUS for women with obesity, metabolic syndrome, or diabetes mellitus, as well as with patients who are young, nulliparous, or at increased risk of thrombophilia. The patient education materials provided by Bayer HealthCare Pharmaceuticals Inc., the manufacturer of the LNG-IUS, use language that may lead patients to question the safety of the device. For example, both the Mirena educational brochure and website instruct patients to “Tell your healthcare provider if you . . . have diabetes . . . [or if you] have problems with blood clotting. . .”<sup>53</sup> Furthermore, the patient education information states, “Mirena is recommended for women who have had at least one child.” Providers should not be unduly influenced by patient fears or the insinuation of risk in package inserts, because evidence-based research has clearly demonstrated the safety of the LNG-IUS for women with diabetes mellitus, women at risk of thrombophilia, and young or nulliparous women.

## Subdermal implant

The etonogestrel-releasing implant is safe (CDC safety category 1 or 2) for women with metabolic syndrome, and it provides the highest efficacy of any reversible contraceptive.<sup>54</sup> This 4-cm subdermal implant releases etonogestrel, a progestin, to prevent pregnancy for as long as three years.<sup>55</sup> With low systemic levels of progestin, contraceptive efficacy is achieved through two mechanisms—ovulation inhibition and thickening of the cervical mucus.

Study of the subdermal implant for potential metabolic effects in women with diabetes mellitus demonstrated a statistically significant reduction of total serum cholesterol, no change in low-density lipoprotein cholesterol (LDL-C) level, and no change in the high-density lipoprotein cholesterol (HDL-C)/total cholesterol ratio.<sup>56</sup> Carbohydrate me-

tabolism was unchanged over the two-year study period, and no aggravation of vascular lesions was noted. Little can be said about metabolic effects of the subdermal implant in women over 130% of ideal body weight, because it has not been prospectively studied in this group.<sup>12</sup>

With appropriate patient selection, continuation rates of the subdermal implant are high. Bleeding irregularity is the main reason for discontinuation in women in the United States.<sup>55</sup> Minimal weight gain (i.e., <3 pounds after 2 years of use), slight increase in acne, and mood alterations are among the adverse effects that lead to implant discontinuation for some women. The ideal patients for the subdermal implant are women who would be tolerant of irregular bleeding patterns and desire the highest contraceptive efficacy available.

## Combined hormonal methods

### *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.<sup>57</sup> 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, the combination of 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.<sup>58</sup> However, only approximately 68% of patients continue combination contraceptive use one year after starting the therapy.<sup>58</sup> 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 reduction of acne, reduction in dysmenorrhea, decreased menstrual flow, suppression of abnormal hair growth, and prevention of ovarian cysts.

For most women with metabolic syndrome, including those with obesity or diabetes, 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 metabolic syndrome in whom vascular comorbidities have developed. In patients who have evidence of end-organ damage, those who have had diabetes mellitus for more than 20 years, and those with systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg or hypertension with coexisting vascular disease, combination therapy is not usually recommended

unless other contraceptive options are not available or acceptable. Table 1 shows CDC/World Health Organization guidelines for assessing contraceptive safety based on individual patient scenarios. Changes in serum lipids, glucose and insulin regulation, and blood pressure have been noted in studies of patients taking combination oral contraceptives. Despite changes in these laboratory and clinical values, it is important to recognize the risks and benefits as they compare with risks associated with unintended pregnancy and other long-term outcomes.

In women with obesity, combined hormonal contraception is safety category 2, meaning that the benefits outweigh the risks. Studies suggest that women with a BMI  $\geq 30$  kg/m<sup>2</sup> using combination oral contraceptives (COCs) have an increased risk of venous thromboembolism (VTE) but no increased risk of myocardial infarction compared with obese nonusers.<sup>59-66</sup> Obesity alone doubles the risk of VTE compared with normal BMI.<sup>59</sup> The absolute risk for VTE is still low. Brunner et al suggests that the risks in obese women using COCs only present a slight increased risk, with five to 10 cases/10,000 nonusers and 15 to 30 cases/10,000 COC users.<sup>67</sup> Despite an increased risk of VTE in the setting of obesity and COC use, multiple studies suggest that pregnancy still poses a higher risk in obese women.<sup>59-61,68-70</sup>

In women with adequately controlled hypertension or ambulatory systolic blood pressures of 140–159 mm Hg or diastolic blood pressures of 90–99 mm Hg, combined hormonal contraceptives are safety category 3, meaning that the condition for which the theoretical or proven risk of using this method usually outweighs the advantages. Thus, women with controlled hypertension who desire combination contraceptive methods over other options should be considered acceptable candidates, and combination contraception should not be withheld. In fact, within the CDC recommendations, it even states that although no data exist, women using COCs with controlled hypertension are less likely to have an acute myocardial infarction or stroke than women with untreated hypertension.<sup>1</sup>

For patients with uncontrolled hypertension—blood pressure exceeding systolic  $\geq 160$  mm Hg/diastolic  $\geq 100$  mm Hg—or in patients with hypertension with vascular disease, combined hormonal contraception is safety category 4 and should not be recommended. Several studies have demonstrated an increased risk for COC users with uncontrolled hypertension; there is an increased risk of stroke, acute myocardial infarction, and peripheral arterial disease.<sup>61,62,71-90</sup> Another study demonstrated a decrease in blood pressure after discontinuing COC.<sup>91</sup> Given this evidence, other contraceptive options should be considered in patients with uncontrolled hypertension or concomitant vascular disease.

Elevation in lipid levels, including total cholesterol, HDL-C, and triglycerides, have been noted in patients using COCs.<sup>92</sup> Current understanding suggests that ethinyl estradiol, found in COCs, enhances the removal of LDL-C and increases HDL-C from the blood while increasing trigly-

erides.<sup>93,94</sup> However, the progestin component found in COCs antagonizes these estrogen-induced lipid effects and causes an increase in LDL-C and decreased HDL-C and triglycerides. Even though the net effect of this combination therapy may increase serum lipid levels, these elevations do not necessarily cause an increased risk of atheromatous plaque formation or demonstrate long-term negative cardiovascular effects or increased mortality.<sup>11,93,94</sup> In patients with known hyperlipidemia, combined hormonal contraception is listed as category 2/3, indicating that it is the role of the physician to evaluate each patient's unique history to determine whether the advantages of therapy outweigh the theoretic or proven risks of this form of contraception. If the lipid status is initially unknown, the CDC does not recommend a routine screen for hyperlipidemia before starting combined hormonal contraception.<sup>1</sup>

Studies show conflicting evidence regarding the effect of combination oral contraceptives on glucose and insulin regulation in the body. Two large studies in the United States have shown that combined oral contraceptives do not contribute to the development of diabetes mellitus.<sup>95,96</sup> Some show that COCs are associated with decreased insulin sensitivity.<sup>92</sup> One prospective study demonstrated an increased fasting glucose in women with well-controlled diabetes but this elevation did not have any other clinical consequences.<sup>97</sup> Metabolic effects seem to vary depending on the progestin component included in the pill. Levonorgestrel has been associated with decreased insulin sensitivity.<sup>98-100</sup> However, pills containing drospirenone, desogestrel, or gestodene tend to be metabolically neutral in terms of carbohydrate metabolism.<sup>101,102</sup> However, in the setting of patients with coexisting diabetic vascular disease, combination hormonal contraception should not be the first option because some evidence suggests that it may accelerate vascular disease in women with diabetes.<sup>103</sup>

As with any clinical decision, both clinical guidelines and individualized risk stratification must be considered when initiating a new contraceptive. Because metabolic syndrome can manifest itself differently in each patient, it is important to consider the effects of combination estrogen-and-progestin therapy on both carbohydrate and lipid metabolism. With careful monitoring and appropriate counseling of patients, physicians should feel confident in prescribing combination therapy to women with metabolic syndrome. Once combination contraceptive therapy is determined to be a safe option, 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, and is considered to be in the same risk category as COCs. There are some differences that are important to understand, however. The steroid hormones in the ring are absorbed directly through the vaginal mucosa, minimizing first-pass metabolism through the liver and causing lower systemic ethinyl estradiol exposure than does oral administration.<sup>104</sup> One advantage of this local hormone administration is that fewer systemic effects have been noted in women with the diseases that comprise metabolic syndrome.<sup>105</sup> Another advantage is the potential for increased compliance for those who find monthly dosing easier to remember than daily dosing.

Similar weight changes were noted after three cycles of using the vaginal ring as oral combination administration.<sup>15</sup> Unlike use of oral contraceptives, no statistically significant change in total cholesterol or HDL-C levels has been noted with use of the vaginal ring; however, a continued elevation in triglyceride levels has been noted.<sup>92,105</sup> The ring has been studied in obese women and no increase in contraceptive failure was noted.<sup>106</sup> Whether a decrease in thrombophilia will be seen with lower exposure to estrogen is yet to be definitively studied. The vaginal ring is an excellent contraceptive method for women with metabolic syndrome who have no vascular disease associated with hypertension or diabetes and who prefer monthly administration, the benefits of an estrogen-containing contraceptive, and a method they can control themselves.

## Transdermal contraception

Transdermal contraception (Ortho Evra) is another option within the category of combination hormonal contraception. It is a contraceptive skin patch that delivers 0.15 mg daily of norelgestromin and 20  $\mu$ g daily of ethinyl estradiol transdermally. With hormone exposure similar to doses found in 35- $\mu$ g combination pills, this method has the expected side effects such as nausea and breast tenderness. Unfortunately, these side effects are seen at higher rates for the transdermal patch than for most oral preparations.<sup>107</sup> The patch is changed once weekly for three weeks. It is then removed to allow for a one-week withdrawal bleed (menses) before placing the next patch. The contraceptive patch is appropriate for women with metabolic syndrome who have no vascular disease and who have a normal BMI and a strong desire for the benefits of an estrogen-containing contraceptive via weekly transdermal administration.

One consideration of patch use for patients with metabolic syndrome is that in clinical trials, women weighing >90 kg (>198 lbs) had a greater failure rate than women with weight <90 kg.<sup>108,109</sup> However, this study pooled data from three multicenter cohort studies and failed to report how much the failure rate was increased or how many women weighing >90 kg were included in the statistical analysis.<sup>108</sup> Concern regarding increased risk of thrombosis is another consideration. One study showed the patch resulted in a more than twofold increased relative risk of VTE in patients without diabetes, compared with use of a 35- $\mu$ g

norgestimate oral contraceptive (40.8/100,000 woman-years in transdermal contraceptive users vs 18.3/100,000 woman-years in norgestimate-containing oral contraceptives users).<sup>110</sup> This study was the subject of much media hype and created significant public concern. It is important to put these risks into perspective for your patients, educating them that the risk of VTE with the patch is still lower than the risk of VTE associated with pregnancy.<sup>70</sup> In comparison, one study estimated the risk of VTE affects five to 12 per 10,000 pregnancies, and three to seven per 10,000 deliveries in the six-week postpartum period.<sup>111</sup>

When making recommendations regarding any of the estrogen-containing contraceptives, one must keep in mind that the standard contraindications to combined hormonal contraceptive use. Both the CDC and the American Congress of Obstetricians and Gynecologists guidelines for contraceptive use emphasize that the following risk factors outweigh the benefits of combination therapies: smoking + age greater than 35 years; uncontrolled hypertension; personal history of stroke; ischemic heart disease or VTE; migraine with aura; and current breast cancer or history of breast cancer, with active disease within the previous five years.<sup>1,57</sup>

## Other progestin-only methods

### Depot medroxyprogesterone acetate injection

Depot medroxyprogesterone acetate is an injectable progestin-only contraceptive that is dosed every three months by intramuscular injection. Although highly effective in preventing pregnancy, DMPA has been demonstrated to produce adverse consequences on carbohydrate and lipid metabolism.<sup>112</sup> 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.<sup>113</sup> The CDC also commented that the effects on lipids demonstrated in DMPA users persist after discontinuation.<sup>1</sup> Several studies have demonstrated that DMPA has no effect on hypertension.<sup>114,115</sup> However, limited studies demonstrate an increase risk for cardiovascular events in women using progestin-only oral or injectable contraception.<sup>116</sup> With regard to glucose regulation, evidence suggests that the use of progestin-only contraception has little effect on short- and long-term diabetes control.<sup>97,117-119</sup> 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 long-standing illness.

### Progestin-only pills

According to CDC guidelines, progestin-only pills (Micronor [norethindrone]; Ortho-McNeil-Janssen Pharmaceuticals Inc.) 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 with metabolic syndrome who have diabetes with or without 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. Although progestin-only pills are safe, adherence with this contraceptive option requires consistent daily dosing, and nonadherence results in significantly decreased efficacy. However, this method still serves as a safe contraceptive choice for women who have contraindications to estrogen while they decide on a long-term option that is less dependent on consistent daily dosing.

### Barrier and behavioral methods

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 following six months, or 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.<sup>120</sup>

### Emergency contraceptive recommendations

Safe to use for patients with diabetes mellitus, emergency contraceptive options (Plan B One-Step [Teva Women's Health Inc, Woodcliff Lake, NJ] and EllaOne [HRA Pharma, Paris, France]) prevent ovulation and are indicated for emergency pregnancy prevention. Containing the progestin levonorgestrel, Plan B One-Step is available over the counter for women older than 17 years. It is available by prescription for younger women. This pill prevents 85% of unintentional pregnancies when taken within 72 hours of unprotected sexual intercourse.<sup>121</sup> EllaOne, containing the progesterone receptor modulator ulipristal acetate, is a newer form of emergency contraception. It is more effective than the levonorgestrel option and provides pregnancy prevention for five days (i.e., 120 hours) after unprotected sexual intercourse.<sup>122,123</sup>

With both emergency contraceptive options, the risks of unintended pregnancy outweigh any actual or theoretical risks of the medications. Patients should be educated on how to obtain emergency contraceptives, and prescriptions

for these pills should be provided to patients using short-term or barrier methods.

### Recommendations for 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 described. A woman may choose from three methods of surgical sterilization—minimally invasive tubal occlusion (Essure [Conceptus Inc., Mountain View, CA] or Adiana [Hologic Inc., Bedford, MA]); 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, but the minimally invasive options of tubal occlusion offer the advantages of fast recovery time, minimal surgical risk, and very high efficacy rates. For women with obesity, laparoscopy is more dangerous than in women of normal weight and the hysteroscopic tubal occlusion procedure is done without incisions and is far less invasive. In addition, hysteroscopic tubal occlusions can be done under local anesthesia in an office setting, even for obese women or women with diabetes. 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 or become the victim of sexual assault.

### Final notes

Contraceptive counseling is essential for women with metabolic syndrome. One study demonstrated that diabetic patients, for example, are less likely to receive such counseling than are nondiabetic women,<sup>124</sup> because physicians are often focused on the management of the diabetes itself. In addition, a recent study also suggests that obese and/or diabetic women are less likely to use contraception or receive preventive health care services compared with women of normal weight.<sup>10</sup> This evidence further stresses the importance that physicians need to address contraceptive choices with their patients who have metabolic syndrome, because use of an appropriate contraceptive carries 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 metabolic syndrome, even those who have advanced disease. In conditions where combined hormonal contraception carries higher risk, many times these risks are reduced or eliminated by using a progestin-only preparation or the LNG-IUS while continu-



ing to provide effective contraceptive benefit. Patients with metabolic syndrome should be counseled about all contraceptive options, including such long-term methods as IUDs and subdermal implants as first-line recommendations.

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