Contraception After Gestational Diabetes

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Women with prior gestational diabetes mellitus (GDM) are at risk of developing overt diabetes, predominantly type 2 diabetes, after pregnancy, often during their reproductive years (1–4). Type 2 diabetes will often be present without symptoms years before the clinical diagnosis is made. Women with type 2 diabetes often do not plan their pregnancy (5) or enter pregnancy with unrecognized diabetes. In both cases, an increased risk of congenital malformations in the offspring has been found (5–7). Similar to type 1 diabetes, this risk has been shown to increase with increasing maternal hyperglycemia (8). Although intervention trials are lacking in type 2 diabetic women, studies in type 1 diabetic women have shown that the proportion of congenital malformations can be reduced to a background population value by prepregnancy planning, including optimization of metabolic control (8). Contraception is an essential component to be able to plan pregnancy when glucose status is normalized and may also confer protection from developing diabetes by preventing a subsequent pregnancy (9). Recent studies show that women with previous GDM exhibit a markedly increased prevalence of the metabolic syndrome, even when glucose tolerance is normal (10,11). Metabolic syndrome is associated with an increased risk of cardiovascular disease and mortality (12).

For both maternal and future offspring, women with prior GDM need safe, efficient, and acceptable choices for contraceptive methods that do not enhance their already substantial risk to develop either overt diabetes or metabolic syndrome and associated sequelae.

Studies on contraception in women with prior GDM are limited, especially new studies published since the Fourth International Workshop-Conference on GDM (13). The present article provides a condensed review of contraceptive methods available for women with prior GDM, focusing on recent studies. When data in women with prior GDM are unavailable, extrapolations will be made from studies in healthy women or from women with diabetes, either type 1 or type 2, who are presumed to have a higher risk of possible complications from contraceptive methods. In all cases, risks of contraception should be compared with pregnancy risk, wanted and unwanted, and risks to future offspring and mother.

BARRIER METHODS — Barrier methods, which include condoms, diaphragm, cervical cap, and spermacides, are well suited for women with prior GDM because of their lack of systemic side effects or influence on glucose tolerance. The typical use annual rate of failure for these methods is in the 20% range. Strong patient and partner motivation and careful instruction detailing proper use may improve contraceptive success. If these criteria cannot be met, intrauterine or hormonal contraception may be better alternatives. The use of condoms should be encouraged in all women with previous GDM who appear at risk for sexually transmitted diseases and human immunodeficiency virus.

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Abbreviations: COC, combination oral contraceptive; DMPA, depo-medroxyprogesterone acetate; GDM, gestational diabetes mellitus; IUD, intrauterine device; POC, progestin-only oral contraceptive.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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INTRAUTERINE DEVICES — The intrauterine device (IUD) is a very effective and reversible contraceptive method without metabolic disturbances and therefore is an ideal contraceptive for women with prior GDM. The 2004 World Health Organization Medical Eligibility Criteria for Contraceptive Use (14) report does not consider prior GDM as a contraindication to IUD prescription. Currently, marked IUDs predominantly contain either copper or levonorgestrel and have not been associated with any increased risk of pelvic inflammatory disease. Both offer excellent pregnancy protection with failure rates below 1%. Their safety is reaffirmed by studies in women with type 1 (15,16) or type 2 (17) diabetes using copper releasing IUDs, which showed no increased risk of pelvic inflammatory disease or failure. The World Health Organization report lists no restrictions on IUD use in either type 1 or type 2 diabetes. The levonorgestrel-releasing IUDs may prove to become a very important contraceptive method for women with a history of GDM because of the very high contraceptive efficacy and the low frequency of bleeding disturbances (18). Furthermore, menstrual bleeding is reduced by progestin-medicated atrophy of the uterine lining, which theoretically would be beneficial in obese glucose-intolerant relatively older and parous women, characteristics common in women with prior GDM. The hormonal release from levonorgestrel-releasing IUDs is low and does not cause significant metabolic effects in normal women (19). So far, no studies have been published with data on the use of levonorgestrel-releasing IUDs in women with a history of GDM. However, a recent randomized trial of the use in women with type 1 diabetes did not show any influence on blood glucose, A1C, or daily insulin dose (20). Therefore, based on the existing evidence, both copper and levonorgestrel-releasing IUDs can be used safely and without any specific restrictions in women with a history of GDM and may be continued if they develop diabetes.

COMBINATION ORAL CONTRACEPTIVES — Combination oral contraceptives (COCs) contain estrogen and progestin and are the most widely

Table 1—*Metabolic effects of hormonal contraceptive methods and components*

	Oral estrogen	Oral progestin	Intramuscular and implants of progestin	IUD
Glucose tolerance	Neutral	↑ Insulin resistance ↑ Glucose tolerance	↑ Insulin resistance ↑ Glucose tolerance	Neutral
Lipids	↑ HDL cholesterol ↓ LDL cholesterol ↑ Triglyceride	↓ HDL cholesterol ↓ LDL cholesterol ↓ Triglyceride	Variable on HDL cholesterol ↓ Triglyceride	Neutral
Blood pressure	Slight ↑	Neutral	Neutral	Neutral
Coagulation	↑ Globulins: dose-dependent ↑	Neutral	Neutral	Neutral

The net effect of COCs varies depending on the various amounts and components of estrogen and progestin used. See text for details.

used type of hormonal contraception. While the estrogen component is always ethinyl estradiol, the type and dose of progestin varies. Generally, ethinyl estradiol has no net effect on glucose tolerance and insulin sensitivity (21) but even the lowest ethinyl estradiol dosage may adversely influence hemostatic and renin-angiotension systems to increase thrombosis risk and blood pressure (22). Ethinyl estradiol also affects lipid metabolism, increasing triglycerides and HDL cholesterol levels and decreasing LDL cholesterol (22,23). The metabolic effects are dose dependent with respect to the amount of estrogen used in the COC. The clinical reason for oral contraceptives to contain estrogen is to improve bleeding control, thereby improving patient compliance. It is important to use the lowest dose possible, or "low-dose COCs" containing 20–35 μg—doses that have proven sufficient to maintain satisfactory cycle control.

The progestin components most widely used in today's COCs are either "second-generation" (e.g., levonorgestrel or norgestimate) or "third-generation" (e.g., desogestrel or gestoden). The third generation progestins have less androgenic side effects. Progestins decrease glucose tolerance and insulin sensitivity. Importantly, progestins have no influence on blood pressure or clotting factors; they may however modify the effects of estrogen by mechanisms still to be elucidated. The progestin effect on lipids tends to antagonize the estrogen effect, i.e., lowering of triglycerides and HDL cholesterol and increasing LDL cholesterol (22,23). The metabolic effects of a given COC formulation will therefore depend on the net effect of the type and/or dosage of each hormonal component. Today's COCs tend to be estrogen dominant. In healthy populations, epidemiological studies in current or previous COC users have not demonstrated an increased risk to develop diabetes (24). Short-term studies have found no clinically relevant detrimental effect on lipid metabolism, and newer COC formulations actually demonstrate a beneficial effect on lipid profiles (22,23). Table 1 outlines the metabolic effects of COCs.

Epidemiological studies

Recent epidemiological case-control studies show that, compared with nonusers, low-dose COC users have an increase in risk of venous and cerebral thrombotic episodes and myocardial infarction (25). A recent large meta-analysis (25) including 14 studies found that current COC users had a twofold increase in summary odds ratio for myocardial infarct and ischemic stroke. Second-generation COCs significantly increased the risk of both arterial events, whereas third-generation COCs continued to increase the risk of ischemic stroke. Compared with nonusers, past use of COCs appeared to be protective of both events. When corrected for other cardiovascular risk factors, the increased risk with COC use persisted. Hypertension, smoking, diabetes, lipid abnormalities, obesity, and family history of arterial events were associated each with an approximate twofold increase in myocardial infarction and a two- to threefold increase in ischemic stroke.

In a second meta-analysis specifically examining COC use in women with preexisting disease, the presence of hypertension per se was associated with substantial risk of cardiovascular events (26). Compared with normotensive nonusers, hypertension without COC use was associated with a 5- to 10-fold increased risk of cardiovascular events, after adjusting other risk factors (i.e., diabetes, lipids, obesity, and smoking). Hypertension with COC use further increased the risk 15- to 68-fold, with the large variation in risk likely due to national differences in screening and treatment of hypertension. Similar to hypertension, COC use in women with a history of migraine was associated with a two- to fourfold increase in stroke compared with nonusers with migraine (26).

The ethinyl estradiol dose in the COC formulation appears to be of greater importance for thrombotic risk than the generation of progestin. A recent population study from Denmark found the risk of cerebral thrombosis with current COC use decreased with decreasing estrogen content and with longer duration of use (27). Compared with nonusers, COCs with decreasing ethinyl estradiol doses of 50, 30–40, 20, and 0 μg (progestin-only oral contraceptive) had corresponding decreasing odds ratios (ORs) of 4.5, 1.6, 1.7, and 1.0 for cerebral thrombosis. The stroke risk was greatest during the first year of use (OR 2.7), decreasing at 1–5 years (OR 2.0) and >5 years (OR 1.8). Theoretically, this decrease in risk might be caused if women susceptible to stroke experienced this soon after starting COCs. These researchers found that after adjusting for the ethinyl estradiol dose, the third- to second-generation progestin stroke risk ratio was 0.6. They also found that the adjusted risk (OR 5.6) from diabetes, irrespective of COC use, was approximately half of the crude stroke risk estimate, suggesting that hypertension was a significant contributor to stroke in diabetic women. In their companion study (28) assessing venous thrombotic risk, COC use compared with nonusers increased the risk three- to fourfold. Similarly, this risk was decreased by decreas-

ing ethinyl estradiol dose formulations and longer duration, with the greatest risk during the first year of use (OR 7.0), decreasing to an OR of 3.1 after 5 years of use. The classic arterial risk factors, hypertension, diabetes, hyperlipidemia, and migraine, did not significantly increase the risk of venous thrombotic events.

How does one apply such epidemiological studies to women with a history of GDM? First, the COC-associated risk must be considered in terms of the low absolute risk of cardiovascular and venous thrombotic events in healthy young women (27,28). The majority of women with prior GDM likely fall into this category and low-dose COC can be prescribed, taking into account that the absolute risks increase with age (27,28). Second, one must consider the magnitude of other risk factors, i.e., hypertension, migraine, smoking, hyperlipidemia, coagulation disorders, and family history of thrombosis, which increase the ORs for arterial and venous thrombotic events by 2- to 12-fold in COC users. Baillargeon et al. (25) argued that prospective studies that examine the relation of cardiovascular events and COC are needed in women with polycystic ovarian syndrome, who are insulin resistant, often obese, and have a high prevalence of cardiovascular risk factors. Women with prior GDM often share these same traits. These risks must be weighed against pregnancy, which itself increases the risk of venous thrombosis fivefold (28). A periodic risk assessment of cardiovascular risk factors in women with prior GDM should be done. When hypertension or migraines are present in women with prior GDM, it would be most prudent to not prescribe a COC. In all cases, the lowest ethinyl estradiol dose should be prescribed and close attention should be paid to increases in blood pressure and weight. All women should receive nutritional counseling, be encouraged to exercise daily, achieve a healthy weight, and receive appropriate medical therapy to control blood pressure and/or lipids if lifestyle interventions fail.

Studies in diabetic women

Short-term studies support low-dose COC prescription in type 1 diabetic women. These studies indicate that the changes in insulin sensitivity, glucose tolerance, lipid metabolism, and the coagulation/thrombotic system are very similar to the findings in healthy women and do not appear to be of clinical significance (22,29). Prescription of COCs does not appear to increase the risk of developing diabetic retinopathy or nephropathy or worse glycemic control (30,31). One recent study has reported an association between COC use and development of macroalbuminuria in women with diabetes (32). The recommendation has been to avoid COC prescription in diabetic women who smoke, are older (>35 years), or have hypertension or diabetes-related vascular complications (33–36).

Relatively few studies on COC use in women with a history of GDM exist (34). Short-term controlled studies of COC use in both Caucasian and Latino women with a history of GDM have not demonstrated any decrease in glucose tolerance or adverse effects on lipid metabolism (37,38) but have found a slight decrease in insulin sensitivity (39). However, such small metabolic changes do not clinically appear to effect the development of diabetes. In a large prospective observational cohort study of Latino women with prior GDM followed for up to 7 years after pregnancy, COC use was not associated with an increased risk of type 2 diabetes compared with similar women not using hormonal contraception (40). Interestingly, women using COCs had significantly less weight gain than nonusers. This report is in line with population-based studies where COC use has not been identified as a risk factor for type 2 diabetes (35,41). More long-term studies in other populations addressing baseline cardiovascular risk factors and outcomes are needed. Furthermore, it is not possible from the present literature to answer the relevant question if COC use in women with previous GDM affects the risk of developing the metabolic syndrome later in life.

In summary, existing evidence from epidemiological and from limited clinical studies in women with diabetes and prior GDM support the prescription of low-dose COCs in women with a history of GDM. Formulations of COC that contain the lowest dose of ethinyl estradiol and the lowest dose/potency progestin should be prescribed following the same recommendations and precautions for healthy women and women with type 1 diabetes. Strong consideration should be given to non–estrogen-containing methods when coexisting hypertension or other cardiovascular risk factors are present.

NONORAL COMBINATION HORMONAL METHODS

— Recently, non-oral combination hormonal methods have become available and can be administered as a monthly injection, a transdermal patch, or an intravaginal ring. Epidemiological data regarding safety or detailed metabolic studies are limited in healthy women. Short-term metabolic studies of the contraceptive patch containing ethinyl estradiol and norelgestromin, the primary active metabolite of norgestimate, suggest that its metabolic effect on lipid profiles (42) and serum androgen levels was predominantly estrogenic and similar to low-dose COCs. Minimal changes in serum lipids were found in short-term use of the vaginal ring containing ethinyl estradiol and norethindrone acetate (43). Studies examining coagulation factors or thrombotic risk with either transdermal methods are not available. One case-control study nested in a cohort of women age 15–39 years with polycystic ovarian syndrome, acne, or hirsuitism specifically evaluated the risk of venous thromboembolism with either COCs or the monthly injectable combination containing ethinyl estradiol and cyproterone acetate (44). In the cohort, the adjusted incidence thrombosis rate in cyproterone acetate/ethinyl estradiol users was significantly elevated compared with conventional COCs (OR 2.58) and with the referent group of healthy, not recently pregnant, non-OC users (OR 7.44). The authors in their study commented that confounding by prescription indication could not be excluded by their study design. In the absence of specific data relating to GDM, the risks/benefits of non-oral combination methods should be considered similar to those of COCs.

PROGESTIN-ONLY ORAL CONTRACEPTIVES

— Progestin-only oral contraceptives (POCs) are taken continuously and contain low-dose norethindrone or levonorgestrel. Progestins do not increase globulin production; thus, they do not increase coagulation factors or blood pressure (45). Their shortcomings are irregular bleeding and the need to be taken daily at strict time intervals, with no "doubling up" on missed days to be effective. Less epidemiological and clinical data are available, since POCs are less widely prescribed than COCs, largely because of their higher actual use failure rates and breakthrough bleeding rates. They are well suited for women with type 1 diabetes where estrogen-containing methods are contraindicated, since they do not influence diabetes control, hypertension, or other vascular dis-

ease (22,33). They also are well suited for women with prior GDM, who often have several cardiovascular risk factors, making non–estrogen-containing contraceptives desirable. Limited studies exist. In a large cohort study (40) in postpartum Latino women, those who were breastfeeding and therefore prescribed POCs were found to have an adjusted threefold increase in the proportion of development of type 2 diabetes during the first 2 years compared with low-dose COC and nonhormonal methods. The risk was increased with duration of POC exposure. With use ≤4 months, there was no increased risk, and with 4–8 months and with >8 months use, there was a threefold increased risk and almost a fivefold increased risk of diabetes. Only breastfeeding women were prescribed POCs in the study, and therefore the question of whether non-breastfeeding women with prior GDM also have any increased risk with POC use could not be answered. The authors speculated that the somewhat surprising finding could be a result of a nonphysiological state that suppressed endogenous estrogen levels from lactation, and exogenous administration of unopposed progestin occurred in unique combination with underlying insulin resistance and a β-cell dysfunction, two hallmarks of GDM. These findings have yet to be confirmed in women of other ethnic backgrounds but indicate that progestin-only pills should not be the first choice of contraception for these women during lactation (40). Progestin-only pills may be used in nonlactating women, especially when contraindications for oral contraceptive use (e.g., hypertension) are present.

LONG-ACTING POC METHODS

— Progestin agents can be administered intramuscularly or subcutaneously as an implant to deliver long-acting and efficacious contraceptive protection. They offer the same metabolic advantage as POC, namely no effect on maternal coagulation factors or blood pressure. There are currently two subcutaneous implants systems: Norplant, with six levonorgestrel rods lasting 5 years, and Implanon, with one etonorgestrel rod lasting 3 years. Norplant is and has been widely used and studied but currently is not marketed in the U.S. Intramuscular progestin compounds include Depo-Provera (depo-medroxyprogesterone acetate [DMPA]), which given every 3 months, or norethindrone, which is given monthly. DMPA has in several studies shown to have more adverse effects on lipids and insulin resistance (46–48) compared with the minimal effects with Norplant (49,50); however, metabolic effects of both methods are clinically insignificant in healthy women. Detailed metabolic studies comparing Implanon and Norplant found comparable and nonsignificant changes from baseline in lipid profiles and apolipoproteins over a 3-year period (51). In contrast to implants, return of fertility after discontinuation can be delayed for up to 9 months with DMPA. DMPA also has been associated with greater weight gain.

Use of long-acting progestins in women with diabetes or women at high risk of diabetes is very limited (48). One study in Navajo Indians found that the use of DMPA increases the risk of diabetes (OR 3.6) compared with women using COCs, and this risk was further increased (OR 8.4) with >1 year of use (52). In contrast, the use of COCs was protective for developing diabetes with OR of 0.59 when adjusted for BMI. These findings are similar to a recent study examining contraceptive use in Latino women with prior GDM (53). In this cohort study, women choosing DMPA had an increased risk of developing diabetes (OR 1.58) compared with women who elected to use COCs. However, women who were prescribed DMPA had significantly more risk factors. When baseline imbalances (BMI, breastfeeding, family members with diabetes, HDL cholesterol, and triglycerides) and weight gain during follow-up were adjusted for, there was no excess risk with DMPA use (OR 1.07; 95% CI 0.61–1.89). The increased risk associated with DMPA appeared to be explained by increased baseline diabetes risk, more weight gain during use, and higher baseline triglycerides and/or breastfeeding. The interaction of DMPA with breastfeeding was similar to that of POC with breastfeeding, adversely effecting diabetes risk (40). Thus, DMPA should be used with caution in breastfeeding women and those with elevated triglyceride levels (>150 mg/dl). Close attention should be paid to weight gain, which also has been demonstrated to increase the risk of subsequent diabetes (9). Studies examining the effect of implant systems on diabetes risk in women with prior GDM are lacking.

Overall, long-acting progestin methods are not a first-line choice in women with prior GDM unless compliance with taking daily medication is a problem. If estrogen-containing contraceptives are contraindicated, the POC would be the first-choice hormonal method or either type of intrauterine device.

SURGICAL STERILIZATION

— Lastly, operative sterilization is an excellent choice for women who have decided that they no longer are interested in childbearing. This option should be offered to parous women, especially those delivering by cesarean section, where the sterilization can be performed during the surgical procedure.

FINAL REMARKS

— Women with prior GDM have many contraceptive options and generally can use all forms of contraception, following essentially the same guidelines as other women. The only significant exception is that progestin-only methods during lactation should be avoided or used with caution. Also, cardiovascular risks and baseline health should be considered when prescribing hormonal methods. In cases of multiple risk factors, a progestin-only method or a metabolically neutral method such as an IUD would be desirable. In all cases, women with prior GDM require effective and safe contraception that suits their lifestyle and does not enhance the risk of developing diabetes, metabolic syndrome, or cardiovascular complications. Regardless of which methods a woman chooses, her care plans should be individualized and should include regular surveillance of glucose tolerance and screening for lipid disorders and other cardiovascular risk factors following standard guidelines. At each visit, blood pressure and weight should be measured and a healthy lifestyle should be reinforced.

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