

# Contraceptive care after gestational diabetes: considerations for clinical practice



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### Practice points

- Gestational diabetes is common, and affected women are at risk of obstetric and medical complications, including subsequent diabetes and cardiovascular disease.
- Postpartum management of women with gestational diabetes must include contraceptive care, since conception of another pregnancy too soon is associated with health risks.
- Use of contraception allows time for planning pregnancies, appropriate spacing of pregnancies and optimization of medical treatments, including weight loss and lifestyle changes.
- Hormonal contraceptives do not negatively affect carbohydrate or lipid metabolism or induce significant weight gain in healthy women, but the data on these effects on obese women or women with abnormal glucose tolerance are unclear.
- Clinicians' recommendations on the most appropriate contraceptive should be based on each woman's medical history, fertility desires and preferences.
- Long-acting reversible contraceptives – IUDs and implants – are highly effective and safe, and may be considered first-line for many women, including those with gestational diabetes.

Gestational diabetes mellitus complicates 6–7% of pregnancies in the USA and increases affected women's risk of developing Type 2 diabetes. Women with diabetes or other medical problems require special attention for reproductive health issues. Women with prediabetes and diabetes are special populations when considering pregnancy risks, postpartum contraception and lifelong health risks. Contraceptive methods differ in composition, mechanisms of action, effectiveness, side-effect profiles, noncontraceptive benefits and safety with specific medical conditions. Hormonal contraceptives do not negatively affect glucose or lipid metabolism in healthy users. While most contraceptives are believed safe in women with gestational diabetes, additional research is necessary to evaluate for glycemic effects. The current review describes clinical considerations for contraceptive care in women with gestational diabetes.

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**KEYWORDS**

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**Background & significance**

Unintended pregnancy is a major public health issue in the USA and abroad. Despite the availability of safe and effective birth control methods in the USA, half of all pregnancies are unintended [1]. Many such pregnancies occur in postpartum women or in women with chronic medical conditions. Repeat pregnancies too soon after delivery are associated with poor obstetric outcomes, including preterm labor, preterm premature rupture of membranes, preterm delivery and low birth weight infants [2,3], as well as increased risks of birth defects and autism [4–6]. Optimal interpregnancy intervals – the time between delivery of one infant and conception of a subsequent pregnancy – are thus necessary to preserve the health of families. Women with medical problems also require special attention with regard to preconception and reproductive health issues, since their co-morbidities may confer higher obstetric risks, pregnancy may be contraindicated or medications used in treatment of their disorders may impose fetal risks. Women with Type 2 diabetes mellitus (T2DM), and those with a history of gestational diabetes (GDM) are a special population when considering pregnancy risks, postpartum contraception and lifelong health risks.

GDM complicates approximately 6–7% of pregnancies in the USA and places affected women at risk of developing T2DM [7–9]. The prevalence of GDM is increasing in developed and developing countries in proportion to rising rates of T2DM and obesity [10,11]. Obesity is an independent risk factor for obstetric complications, including GDM, hypertensive disorders, cesarean delivery, premature delivery, fetal anomalies, labor dystocia and fetal macrosomia, and infants of obese mothers are at risk of childhood obesity [12]. Additionally, obese women are at risk of long-term health complications including cardiovascular disease, diabetes, orthopedic conditions and cancer [13,14].

Women with prior GDM or T2DM may experience an unintended pregnancy or conceive with undiagnosed diabetes, increasing maternal morbidity and obstetric complications [15]. Women with T2DM experience an increased risk of fetal malformations, and the risk of congenital anomalies increases with worsening maternal hyperglycemia. However, with optimal glucose control near the time of conception, the rate of major birth defects in these women is reduced to that of the general population [16].

Effective contraception is thus critical for delaying pregnancy until euglycemia is achieved, and evidence suggests that contraception decreases the risk of developing T2DM by preventing a subsequent pregnancy [17]. Previous GDM predisposes a woman to development of T2DM, with an estimated risk of 35–60% of T2DM within 10 years [9].

Modern contraception allows women with medical problems, including obesity and GDM or T2DM, to plan or avoid pregnancy. Contraceptive use affords time for optimization of medical treatments, which can directly improve maternal and infant outcomes. The choice of the best contraceptive depends on several factors, including medical history, current medication use, desire for future fertility, compliance and acceptability.

Despite our knowledge of the health risks associated with GDM and our recognition of the important role of contraception, clinical practice and research lags behind our patients' needs. Providers frequently fail to recognize previous GDM as a disease state requiring close attention. Primary care providers, obstetricians and endocrinologists must emphasize the need for pregnancy planning, weight reduction, disease control and contraception when caring for this high-risk population of women.

**Overview of contraceptive methods**

Use of effective contraception reduces unintended pregnancy and its associated consequences. Contraceptives may be classified based on their medication content, route of administration or duration of action. Frequently, contraceptive methods are divided into groups based on whether or not they contain hormones, the types of hormones contained and by their failure rates (Table 1).

Contraceptive failure rates are defined as the percentage of users who will become pregnant over the course of 1 year. This rate is subdivided into 'perfect use' and 'typical use'. Perfect use refers to the *in vivo* failure rates demonstrated when each method was taken correctly and consistently. Failure rates demonstrated in clinical trials approximate perfect use. Typical-use failure rates take into account when users fail to use a method consistently or use it incorrectly; this rate reflects use under 'real-world' circumstances. The first-year failure rate with typical use is the clinically relevant measure, when comparing contraceptive effectiveness. Pregnancy

**Table 1. Contraceptive methods available in the USA.**

Contraceptive method	Composition	Description of correct use	Frequency of administration	Typical use failure rate (%) [18]
Diaphragm	Latex or silicone Nonhormonal barrier	Place in vagina up to 6 h before intercourse, and remove no sooner than 6 h after intercourse, up to 24 h	During coital episode	12
Male condom	Latex or non-latex Nonhormonal barrier	Use each condom only once, with every coital episode	One coital episode	18
Combined oral contraceptives	EE (usually 20, 30 or 35 µg) and progestin (various types and doses)	Standard dosing: use for 28-day cycle, active pills on days 1–21, placebo pills on days 22–28 Extended-cycle dosing: varies, use active pills continuously, with occasional 7-day placebo periods	Daily pill	9
Combined hormonal vaginal ring	EE 15 µg and etonogestrel 120 µg	Use for 28-day cycle, vaginal ring placed for days 1–21, removed for days 22–28	Monthly vaginal ring	9
Combined hormonal contraceptive patch	EE 20 µg and norelgestromin 150 µg	Use for 28-day cycle, one patch placed every 7 days for days 1–21, no patch worn on days 22–28	Weekly patch	9
Progestin-only pills	Norethindrone 35 µg	Use continuously, one pill taken at the same time every day	Daily pill	9
Progestin injection	Depot medroxyprogesterone acetate 150 mg	Intramuscular injection by medical professional	12–14 weeks	6
Progestin implant	Etonogestrel 68 mg	Subdermal implant placed by certified medical professional	3 years	0.05
IUDs	Levonorgestrel 13.5 or 52 mg Copper, nonhormonal	Placed in uterus by medical professional	3–5 years (depending on specific device) 10 years	0.2 0.8
Sterilization	Nonhormonal	Blockage, transection or removal of fallopian tubes	Permanent; lifetime	0.5

EE: Ethinyl estradiol.

rates during typical use reflect contraceptive effectiveness for the average person who does not always use methods correctly or consistently. Typical use does not imply that a contraceptive method was consistently used.

#### • Barrier methods

Barrier methods, in other words, condoms and diaphragms, are nonhormonal forms of contraception that provide protection against pregnancy and sexually transmitted infections (STIs).

Male latex condoms provide protection against STIs when used correctly and consistently, and are the most effective method to reduce STI transmission [19]. Unfortunately, condoms typically provide less protection against pregnancy than other contraceptive methods, since they are coitally dependent and prone to user error or nonuse.

A diaphragm is a dome-shaped device, made of latex or silicone, placed in the vagina by the

woman prior to intercourse. In motivated users, the diaphragm offers quite effective nonhormonal contraception and moderate protection from STIs. Traditionally, clinicians have recommended concurrent use of a spermicide with the diaphragm, but this practice is not supported in the literature [20].

#### • Combined hormonal contraception

Combined hormonal contraceptives (CHCs) contain an estrogen and a progestin, administered orally, transvaginally or transdermally. These popular contraceptives are the most commonly used by women in the USA, chosen by approximately 10 million women yearly. Current formulations of the combined oral contraceptive (COC), contraceptive vaginal ring and transdermal contraceptive patch contain an estrogen component (most commonly, ethinyl estradiol) and one of several different progestins. The oral contraceptive is the most common reversible

birth control method, used by 25.9% of all contraceptive users and 16% of all women of reproductive age [21].

CHCs prevent pregnancy by suppression of ovulation via inhibition of gonadotropin secretion from pituitary and hypothalamic centers. The progestin suppresses secretion of luteinizing hormone, and the estrogen suppression of dominant follicle emergence through follicle-stimulating hormone inhibition [22]. The standard dosage cycle for CHCs mimics a 28-day spontaneous menstrual cycle; 21 days of active hormone, followed by 7 days of placebo. For COCs, women take pills for 21 consecutive days, then experience a withdrawal bleeding episode during the placebo week. Extended-cycle formulations involve using active hormone pills for longer intervals, often 12 weeks, followed by a hormone-free week for withdrawal bleeding. The contraceptive ring is used for 21 days, then removed for a 7-day period, during which withdrawal bleeding ensues. The contraceptive patch is applied weekly, with use of 3 weekly patches, followed by a patch-free withdrawal week.

Most current COCs contain 20–35 µg of ethinyl estradiol. Several COC formulations, containing various low doses of ethinyl estradiol combined with one of many different progestin types and doses, are available today. In the USA, one vaginal ring (NuvaRing®, Merck, NJ, USA) and one transdermal patch (Ortho-Evra®, Janssen, NJ, USA) are available (Table 1).

Combined hormonal methods offer several noncontraceptive benefits, including cycle control, relief from dysmenorrhea, treatment of endometriosis, treatment of premenstrual syndrome or dysphoric disorder, improved acne and hirsutism, increased bone mass, ovarian cyst suppression, and decreased risk of ovarian and endometrial cancers. Many women benefit from these effects, in addition to pregnancy prevention.

#### • Progestin-only pills

The progestin-only pill (POP), often called the ‘minipill,’ is an oral contraceptive containing progestin alone, without an estrogen component. In the USA, the POP contains norethindrone 35 µg. In Europe, POPs composed of various progestins, including desogestrel, levonorgestrel and norethisterone, are available.

The POP exerts its major contraceptive action by thickening of the cervical mucus. Other mechanisms include ovulation suppression through gonadotropin inhibition and

alteration of the endometrium environment. Gonadotropin suppression is inconsistent and pregnancy prevention depends more on the other progestin effects. Progestin effects on cervical mucus require 2–4 hours to take effect and wane by 22–24 hours. Thus, POPs must be taken daily at the sametime every day (no hormone-free days) for optimal contraceptive efficacy. The typical failure rate for the POP is 9%, the same as that for COCs [19–23].

Since they lack estrogen, POPs are suitable for women with contraindications to estrogen-containing products, including women with severe hypertension, history of venous thromboembolism or history of stroke, who choose to use an oral contraceptive. The minipill is also commonly used by lactating women.

#### • Injectable contraception

Depot-medroxyprogesterone acetate (DMPA) or Depo-Provera® (Pfizer, NY, USA), is a progestin-only contraceptive administered as an intramuscular injection. DMPA is a popular contraceptive worldwide, and is used by millions of women in developed and developing countries. DMPA relies on rhythmic peaks in hormone release for ovulation inhibition, endometrial involution and cervical mucus thickening for pregnancy prevention. DMPA is highly effective if used consistently, with a perfect-use failure rate of 0.2%. However, the typical-use failure rate is 6%, mostly attributable to noncompliance with office visits for quarterly dosing.

DMPA is a potent inhibitor of gonadotropin secretion and ovulation, and thus offers a high rate of amenorrhea, preferred by many users. Noncontraceptive benefits include decreased menstrual bleeding, treatment of dysmenorrhea and prevention of ovarian cyst formation. Adverse events include irregular bleeding (most common in the first few cycles of use) and decreased bone mineral density. Effects on bone density are reversible after discontinuation of DMPA, and concerns for bone loss in healthy women should not limit its provision [23].

#### • Contraceptive implant

The subdermal contraceptive implant available in the USA is a single, nonbiodegradable, progestin-only rod that contains 68 mg of etonogestrel (Nexplanon®, Merck). The implant is placed under the skin of the upper arm and palpable but rarely visible. Daily etonogestrel release provides contraception through ovulation suppression,

endometrial thinning and cervical mucus thickening. Other progestin-only implants are available worldwide, containing levonorgestrel.

The implant is a long-acting reversible contraceptive (LARC) method, characterized by superior effectiveness and little dependence on the user for maintenance. LARC methods, the implant and the IUD, are the most effective contraceptive methods, since failure rates with typical use resemble those of perfect use.

The major adverse event with the subdermal implant is irregular bleeding. Approximately 20% of women experience frequent or prolonged bleeding, which can lead to discontinuation. However, many users enjoy amenorrhea or regular light menstrual bleeding [24].

#### • Intrauterine contraceptives

The other LARC method, the intrauterine device (IUD), provides highly effective contraception for 3–10 years, depending on the specific device chosen. Recent estimates demonstrate that approximately 10% of US contraceptive users used the IUD in 2012 [21,25].

Four IUDs approved by the US FDA are currently available in the US market. The TCu-380A, or Paragard® (Teva, PA, USA), is a copper IUD approved for 10 years of use. The TCu-380A contains no hormones. Contraceptive effect occurs via release of free copper and copper salts, which create a biochemical and morphologic impact on the endometrium, endometrial secretions and cervical mucus. A potent spermicidal effect results from these biochemical and morphologic changes that prevent fertilization [22]. The copper IUD is highly effective, with a typical-use failure rate of 0.8%. Since it is hormone-free, the copper IUD is an ideal option for women desiring reliable contraception who have contraindications to hormonal products or who prefer a nonhormonal method. Menstrual cycles are unchanged from baseline, and some women experience heavier menstrual bleeding, although clinically significant menorrhagia is rare.

The hormone-releasing IUDs are progestin-only methods and contain levonorgestrel. The systems differ in either the concentration of daily levonorgestrel release or approved duration of use (3–5 years). These IUDs are marketed under the brand names of Skyla®, Mirena® (Bayer, PA, USA), and Liletta® (Actavis, NJ, USA and Medicines360, CA, USA). The latter two devices contain 52 mg of levonorgestrel, released

at 14–20 µg daily. The Skyla is a lower-dose, smaller IUD, containing 13.5 mg levonorgestrel released at 5–14 µg daily. Contraceptive effects of the levonorgestrel IUDs result from local progestin endometrial involution and cervical mucus thickening. These IUDs are highly effective, with failure rates of 0.2% [18].

The levonorgestrel IUDs exert a potent effect on the endometrium, and thus provide a favorable bleeding profile. These IUDs confer a high rate of amenorrhea and light menstrual bleeding. Progestin IUDs offer several non-contraceptive benefits, including treatment of menorrhagia, endometrial protection for women with anovulatory cycles or those using estrogen hormone replacement therapy, and relief from dysmenorrhea.

#### • Sterilization

Female surgical sterilization is the most prevalent contraceptive method worldwide and the method most commonly chosen by women aged 30 years and older in the USA [25]. Female surgical sterilization is accomplished through a transabdominal or transcervical approach.

Traditionally, tubal interruption is performed at the time of delivery (postpartum tubal ligation) or remote from pregnancy (interval sterilization). Modern interval sterilization procedures are generally performed through laparoscopic tubal interruption (most commonly with surgical clips, silicone bands or bipolar cauterization) or bilateral salpingectomy. Tubal ligation is highly effective, with failure rates of approximately 7–15 per 1000 procedures [26,27], or approximately 0.5% [18].

Transcervical sterilization via hysteroscopy (Essure®, Bayer) was FDA approved in 2002 and offers a minimally invasive means of permanent sterilization. These procedures are performed in the office setting and require little or no anesthesia. The tubal ostia are visualized using a hysteroscope, and using a specialized catheter, micro-insert coils are inserted into the proximal portion of each fallopian tube. The micro-inserts induce a benign, localized tissue-in-growth process inducing occlusion of the tubal lumen and permanent tubal blockage [28]. Complete occlusion occurs over 3 months and is confirmed using a hysterosalpingogram. Back-up contraception is necessary during the 3-month period between the procedure and hysterosalpingogram. Failure rates for women confirmed tubal occlusion are low,

estimated at less than 0.5% [28], although real-world estimates of failure rates may be higher and are somewhat unclear, based on current data.

### Benefits of long-acting reversible contraception

LARC methods are the most effective means of pregnancy prevention. The low failure rates exist because the IUDs and implants require no ongoing effort by the user to produce continued effective use. Lack of active adherence removes the problem of incorrect or inconsistent use of a contraceptive method, both of which most commonly lead to unintended pregnancy. Other characteristics of LARC methods include favorable safety profiles, rapid return to fertility after discontinuation, cost-effectiveness, relatively few contraindications for use and associated noncontraceptive benefits.

Use of implants and IUDs in adolescents and adult women is supported by the American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics. Both professional societies recommend LARC as a first-line option for many women and girls [29,30].

The public health impact of LARC use was recently demonstrated in a prospective study. The Contraceptive CHOICE Project, a research initiative in St. Louis, Missouri, USA evaluated whether rates of unintended pregnancy could be improved with increased uptake of LARC. Over 9000 women and girls received directed contraceptive counseling and their choice of method, free of charge. A total of 75% of participants chose a LARC method. The central publication from this study documented 20% lower repeat abortion rates in the St Louis area compared with other parts of the state, and markedly lower teen pregnancy rates in CHOICE participants, compared with national statistics [31]. The study findings suggest that when the barriers of cost, knowledge and access were removed, LARC use carries the potential to reduce the number of unintended pregnancies. The CHOICE project also found that LARC users were more likely than users of other contraceptives to continue use at 12, 24 and 36-month follow-up (86 vs 55%, 77 vs 41% and 69.7 vs 28.2%, respectively), and that non-LARC users were over 22-times more likely to experience an unintended pregnancy, compared with their LARC counterparts [32].

### Metabolic effects of hormonal contraceptives

The impact of hormonal contraceptives on lipoproteins and carbohydrate metabolism has been extensively studied. Early studies showing unfavorable effects on lipid and carbohydrate levels mostly included oral contraceptives containing high doses of synthetic estrogens and progestins, which are uncommon in today's preparations. However, understanding the metabolic effects of modern contraceptives remains important, especially in users with cardiovascular disease or insulin resistance, such as women with a history of GDM or prediabetes.

#### • Effects on lipid metabolism

Generally speaking, estrogens induce a favorable lipid profile, while progestins negatively impact cholesterol and lipoprotein levels. The balance of estrogen and progestin potency theoretically affects lipoprotein levels and potentially negatively impacts cardiovascular health. The currently available CHC products do not impose a clinically significant impact on cardiovascular risk. Ethinyl estradiol has been shown to increase the production of very low-density lipoprotein, high-density lipoprotein (HDL) and triglycerides, and to decrease low-density lipoprotein (LDL) production [33–35]. In contrast, progestins with their androgenic properties tend to increase LDL and triglycerides and lower HDL.

Data from clinical trials suggest that current COCs containing low-dose formulations of less androgenic progestins, such as desogestrel, dienogest and drospirenone, confer a favorable effect on the lipid profile, including increases in mean HDL levels [36,37]. COC formulations with progestins that are traditionally associated with more androgenicity, such as levonorgestrel, produce short-term negative changes in the lipid profile, including increases in LDL, but with reversion to baseline levels after 1 year [38]. When reviewing these data, it is important to note that there is no evidence of atherosclerosis leading to subsequent cardiovascular risk in CHC users.

Based on the negative effects on lipids imposed by progestins, researchers have hypothesized that women using progestin-only pills would have less favorable lipid profiles. However, clinical data do not support this hypothesis, and research findings are reassuring with regard to the impact of POP on cholesterol and lipoprotein metabolism. One study measured lipids in participants using one of two different POPs, desogestrel

and levonorgestrel, and found no clinically significant changes in lipid parameters and no measurable differences between groups [39].

Clinical studies evaluating the effects of DMPA on lipid metabolism demonstrate somewhat mixed results. Some trials report negative effects on lipids, such as increased LDL and triglyceride levels or changes in HDL, but sample sizes were relatively small and findings varied by length of DMPA use [40–42]. There is no evidence suggesting that, even if lipid metabolism is impaired in DMPA users, the risk of subsequent atherosclerosis or cardiovascular events is elevated [43].

Data evaluating lipid metabolism in etonogestrel implant users show no clinically significant effect of the implant on lipid parameters. Changes in total cholesterol, HDL, LDL or triglycerides were modest and levels typically remained within normal ranges. One study reported a trend toward increased total cholesterol and triglycerides, and no changes in LDL or HDL after 3 years of use [44], with all values remaining in normal ranges. A second study, which evaluated lipid metabolism with implant use in the first 12 weeks postpartum, demonstrated normal-range reductions in all parameters, cholesterol, triglycerides, LDL and HDL [45]. Another study compared lipid levels in obese users of the etonogestrel implant, levonorgestrel IUD and nonhormonal contraceptives. Levels were unchanged and similar between groups at 6 months of use [46].

Use of the levonorgestrel IUD unlikely impacts the lipid profile in a clinically relevant fashion, based on available data. One large-scale cross-sectional study reported comparable lipid profiles in levonorgestrel IUD users and nonhormonal contraceptive users who were 40–42 years old [47]. Other studies report similarly reassuring findings [46,48].

#### • Effects on insulin sensitivity & glucose metabolism

Synthetic progestins have been shown to reduce tissue insulin sensitivity, leading to a compensatory increase in insulin release following a glucose load [49,50]. The magnitude of the effect is dose-dependent and is possibly compound-specific, with higher concentrations of the more androgenic progestins bestowing a greater affect compared with lower concentrations and less androgenic progestins [50]. Synthetic estrogens likely induce the opposite effect; research

suggests that ethinyl estradiol improves insulin sensitivity [51,52].

A 2009 Cochrane review evaluated the effects of hormonal contraceptive on carbohydrate metabolism and concluded that COCs have no consistent nor relevant effect on glucose metabolism in women without diabetes [53]. Data on the other CHCs, the vaginal ring and the transdermal patch, also demonstrate no effect on insulin sensitivity [54].

Considering the progestin-induced alterations in insulin sensitivity, it was appropriately hypothesized that progestin-only pills would decrease insulin sensitivity and impair glucose tolerance, predisposing a POP user to subsequent prediabetes or T2DM. However, research demonstrates no such impairment, and hyperglycemia is not a clinical concern with POP use in the healthy general population. In one study, women randomized to either a desogestrel or levonorgestrel POP formulation exhibited no clinically significant alterations in insulin sensitivity or carbohydrate metabolism. Additionally, no alterations in glycosylated hemoglobin values were found at long-term follow-up, suggesting no increase in downstream T2DM risk [55].

Epidemiologic and analytic studies have examined the effects of DMPA on carbohydrate metabolism. In a case–control study of Navajo women, DMPA users had a 3.6-fold increased odds of developing diabetes, compared with COC users [56]. The majority of the participants were overweight or obese, with a mean BMI of 30.6 kg/m<sup>2</sup> in the study population. Other studies report similar findings, demonstrating significant elevations of serum insulin concentrations and decreased glucose tolerance among overweight and obese DMPA users [42,57–58]. These studies did not find a similar effect of DMPA on glucose concentrations in lean, glucose-tolerant women. Worsened glycemia only involved DMPA users who were heavier at baseline (mean weight ≥68 kg), suggesting that body weight prevails as the risk factor in glucose impairment and subsequent diabetes, rather than use of DMPA [57,58].

Research findings show that the etonogestrel implant can reduce insulin sensitivity by up to 30% in healthy women [54] and raise fasting serum glucose levels at 24 months of use [59]. However, serum levels of insulin and glucose remained within normal ranges, so the changes are clinically irrelevant in the general population of healthy users. In obese women, these

changes may impart clinical significance. A study evaluating the effects of the etonogestrel implant compared with nonhormonal contraceptives on metabolic markers in obese women demonstrated statistically significant increases in fasting glucose levels in implant users. Fasting glucose levels reached an average of 101 mg/dl, 6 months after initiation of the implant, which meets the American Diabetes Association criteria for prediabetes [46]. These results further suggest an association between weight and diabetes risk, rather than progestin use and hyperglycemia. Data from the same study showed that levonorgestrel IUD users had modest elevations in fasting glucose levels, but the values remained below the threshold for diagnosis of prediabetes.

#### • Effects on body weight

Concern about weight gain may dissuade women from the use of effective hormonal contraception, impairing initiation of use and causing early discontinuation among users [60–62]. However, a causal association between CHCs and weight gain has not been established.

Observational studies and clinical trials have examined weight gain in COC users. The vast majority document little or no weight gain in COC users, either when followed over time, or when compared with controls or users of other hormonal or nonhormonal contraceptive methods [63–65]. Studies suggesting weight increases demonstrated weight gain of small magnitude, less than 2 kg per year.

A 2014 Cochrane review reported the results of 49 trials comparing weight gain in CHC users with another hormonal contraceptive method, or with placebo or no hormonal method. A variety of COC formulations, the vaginal ring and the transdermal patch were included in the reviewed trials. The comparisons of a combination contraceptive with a placebo or no hormonal method showed no significant differences in weight change [66]. These included only five comparisons between a COC and a placebo [67], or no intervention [68,69], and one comparison between a transdermal patch and placebo [70]. Data from the four trials with a placebo or no intervention group did not suggest a causal association between COC or transdermal patch and weight change. Most comparisons of different combined hormonal methods showed no substantial difference in weight. The authors concluded that the current evidence was insufficient

to clearly establish the effect of CHCs on weight, but no large effect was evident.

Even more so than with CHCs, concern exists among clinicians and patients about weight gain on DMPA. Many investigators have assessed weight gain in women using DMPA, and the data are mixed, with some reports suggesting quite extensive weight gain and others showing no association.

A 2013 Cochrane review examined the evidence for weight change on progestin-only methods of contraception. Of 16 included studies, ten assessed body weight and body composition in DMPA users. In three studies, body mass changes were compared in DMPA users and users of other hormonal methods, or DMPA plus an estradiol-containing supplement [71–73]. Changes in weight between the DMPA users and comparison groups were similar, and no major weight increases were detected, although one study did note an increase in total body fat and decrease in lean body mass in adolescent DMPA users [71]. Five studies compared weight gain with different dosing regimens of DMPA [74], DMPA initiation in the postpartum period compared with interval initiation [75], or compared DMPA with norethisterone enanthate, another progestin-only injectable [76]. No differences in weight change between groups were detected in any of these comparisons. In two trials, weight gain in DMPA users was compared with that in nonhormonal IUD users. One study showed no difference in weight gain between groups [77], while the other demonstrated that mean weight gain in DMPA users was approximately 2–3 kg more than in nonhormonal IUD users, measured at 1, 2 and 3 years of use [78]. Overall, the review presents limited evidence of weight gain when using progestin-only contraceptives, although some studies do suggest modest increases in weight gain in DMPA users, compared with nonhormonal contraceptive users.

One area of potential concern regarding DMPA and weight gain, however, is weight change in adolescents who are already obese at DMPA initiation. Studies suggest that overweight or obese adolescent DMPA users may gain more weight than normal-weight users. This association is not evident in adults [79].

Overall, the current literature remains unclear about the association between DMPA and weight gain. In most cases, weight gain secondary to DMPA use is modest, and may not



be remarkably different than usual changes in weight experience by women over time. Given the lack of data suggesting pathologic weight gain, DMPA should not be avoided for concern over weight gain alone in most adult women.

#### • Effects on blood pressure

Hypertension induced by COC use was traditionally noted in women on pills containing 50 mcg or more of ethinyl estradiol. Increases in blood pressure can also occur with today's lower dose formulations, but the majority of these changes are small and not clinically significant [22,80–81].

While blood pressure changes resulting in clinically significant hypertension are rare in healthy users, women with pre-existing hypertension or those who develop essential hypertension while using a CHC should be monitored. Blood pressure management should follow the usual treatment algorithms, with lifestyle changes including diet and exercise, and medication when indicated. If adequate control of blood pressure cannot be achieved, clinicians should consider discontinuation of the CHC [82] and initiation of a progestin-only or nonhormonal contraceptive.

#### Recommendations for clinical practice

Women benefit from use of effective contraception, since prevention of pregnancy, timing of pregnancy and birth spacing are important medical, social and family issues. The choice of contraceptive method must be tailored to each woman's unique needs. Considerations include medical co-morbidities, compliance, cost, noncontraceptive benefits and plans for future pregnancies.

Women with previous GDM frequently have other medical issues to consider when prescribing contraception. Women with GDM may be obese and may have co-existing hypertension or other cardiovascular disorders. The appropriateness of a contraceptive method will vary, based on the type of medical problem and its severity, balanced against the risk of unintended pregnancy in each patient. Women with past GDM are a special population, because the diagnosis of GDM signals an underlying metabolic derangement. Women with glucose intolerance unmasked by pregnancy are at risk of development of subsequent T2DM, and the ideal contraceptive is one that will not heighten or accelerate this risk.

#### • Contraception in the postpartum period

Early initiation of contraception after delivery is important for prevention of unintended pregnancy and short interval birth. The postpartum period is an important time to initiate contraception because women may have increased motivation to avoid another pregnancy and because access to healthcare is routine at that time. Ovulation can occur as early as 25 days postpartum [83] among non-breastfeeding women, so initiating contraception in the early postpartum period is critical.

A discrepancy exists between the diagnosis and treatment of GDM during pregnancy and recognition of its implications beyond pregnancy. Upon delivery of the infant, obstetric providers frequently view the GDM as a resolved condition. While most obstetricians follow recommendations for ordering glucose tolerance tests 6 weeks postpartum, beyond that time, the OBGYN does little to consider the implications of the GDM diagnosis on future healthcare. Primary care providers also fail to recognize the importance of past GDM as an identifiable risk factor for T2DM.

In the postpartum period, the choice of contraceptive will depend on additional factors, such as lactation status, mode of delivery (vaginal or cesarean delivery), age, pre-eclampsia, smoking and other factors related to risk of venous thromboembolism [84]. Additionally, concerns regarding compliance, cost and access to care can impact contraceptive recommendations. In the early postpartum period – generally considered the first 6 weeks – consideration of other obstetric and postpartum factors are in play, and specific guidelines denote the timing of the initiation of CHCs. Generally speaking, CHCs are safely started 21–42 days postpartum in non-lactating, nonsmoking, normal-weight women under the age of 35 years, with a vaginal delivery and no other risk factors for thrombosis. In healthy breastfeeding women without any of the listed risk factors, CHC initiation can occur 30–42 days postpartum. If one or more risk factors exist, delaying initiation to 30–42 days postpartum may be recommended [84].

Since venous thromboembolism risk returns to baseline after 6–12 weeks postpartum, any contraceptive method can be safely used after that time in healthy women. Having had GDM alone does not change this recommendation, so women with recent GDM but no other medical conditions are candidates for all contraceptives [82,84].

Progestin-only pills are commonly used by lactating women. There is no theoretical or proven impact on breastmilk supply or infant development, and the absence of estrogen allows immediate postpartum initiation. Since POP does not affect thromboembolism risk or lactation, they can be safely initiated immediately postpartum in breastfeeding and non-breastfeeding women. Similarly, progestin implant and IUDs can be safely used postpartum, and offer the added benefits of LARC – namely, low failure rates and little user error. IUD placement may occur immediately after delivery (post-placental insertion), or 4 to 6 weeks postpartum, without substantially increased risks of expulsion. IUD placement beyond the first few minutes of placental delivery up to the first 4 weeks postpartum (delayed postpartum insertion), however, should be exercised with caution, since expulsion rates are higher than acceptable in many clinical settings. Etonogestrel implants are safely used in lactating and nonlactating women at any time postpartum, and bestow LARC benefits without the risk of expulsion seen with IUDs.

#### • Clinical guidelines & basis of recommendations

In 2010, the CDC issued the US Medical Eligibility Criteria for Contraceptive Use (MEC) [82], a set of guidelines for clinical use when prescribing contraceptives. This document was adapted from the WHO's MEC, first published in 1996. The basis of the MEC is that most women are candidates for safe use of all types of contraceptive methods, but women with certain medical conditions may carry relative or absolute contraindications to certain methods. These medically complicated women are those who may have the most need for contraception, since an unplanned pregnancy could present major health risks. The MEC lists medical conditions or patient characteristics (i.e., hypertension, venous thromboembolism, age, smoking) and rates the appropriateness of each contraceptive method for each condition or characteristic. The safety of the method is assigned a category rating, from 1 to 4. The MEC categories and definitions are shown in **Table 2**. Both the WHO MEC and the CDC MEC assign category 1 ratings to all contraceptives in women with GDM.

Two caveats are important in applying these recommendations to clinical practice. First, the MEC rating system evaluates the safety of each

contraceptive type when used in a patient with a specific medical disorder or characteristic. The category ratings do not account for efficacy or effectiveness, made apparent by barrier contraceptives having a category 1 rating for nearly all conditions. In practice, recommending a barrier method alone to be used by a woman with a severe medical disorder, such as cardiomyopathy, could result in a high-risk unintended pregnancy. Furthermore, responsible contraceptive provision requires that effectiveness be included in counseling and recommendations. The risk of pregnancy due to failure of barrier contraceptives is sufficiently high that most women – healthy or medically complicated – are better served by more reliable methods.

The second caveat is that the MEC recommendations are based on the best available evidence, which does not necessarily equate to complete data, a robust body of research or high-quality evidence, for all listed conditions. The category 1 ratings for history of GDM are appropriate, based on the available evidence. Study findings are consistent with one another, and most demonstrate little or no concern for use of each contraceptive in women prior GDM alone. However, the available research is relatively scant, and there is little direct prospective evidence.

#### • Contraception & subsequent T2DM in women with gestational diabetes

Evidence supports the safety of hormonal contraceptives in healthy women, with no increased metabolic risks. Changes in glucose metabolism or insulin sensitivity are minimal and not clinically significant. The magnitude of these effects and their outcomes in women with potentially abnormal glucose tolerance, such as obese women, women with metabolic syndrome and women with GDM, has not been elucidated.

The optimal contraceptive methods for women with a history of GDM remain unknown, and a recent study showed that women with GDM choose similar methods as those not affected with GDM [86]. Limited studies address the use of COCs in women with prior GDM, but the available evidence supports their use [87–89]. Data on nonoral CHCs (vaginal ring and transdermal patch) are similarly limited. Since these agents create similar metabolic effects as combined pills, the ring and patch are generally considered safe in women with previous GDM [90].

The POP and DMPA are commonly used postpartum, and are good options for healthy

**Table 2. CDC Medical Eligibility Criteria for Contraceptive Use classification system.**

Classification (category)	Definition
1	No restriction for use of the method
2	The advantages of using the method generally outweigh the theoretical or proven risks
3	The theoretical or proven risks usually outweigh the advantages of using the method
4	An unacceptable health risk if the method is used

Data taken from [85].

women. However, the effect of progestin-only contraceptives on subsequent prediabetes and diabetes in women with GDM is unclear. Some evidence suggests increased risk of development of T2DM in women with GDM with use of these methods. A summary of relevant study findings is shown in **Table 3**.

One retrospective cohort study of Latina women with GDM using POPs reported a relative risk of 2.87 (95% CI: 1.57–5.27) of developing T2DM over 7.5 years, compared with women using barrier or combined hormonal methods [91]. In this study, charts of 904 women with GDM were reviewed, with 443 women using nonhormonal contraception, 383 using COCs and 78 breastfeeding women using POP, each method initiated 4–16 weeks postpartum. The rates of progression to T2DM up to 7.5 years postpartum in each group were 8.7, 10.4 and 26.5%, respectively. The apparent association between POP use and development of T2DM are compelling, but sample size, heterogeneity of the follow-up time period, and baseline differences between POP users and COC users must be considered. POP users had higher parity, BMI and cholesterol levels, and had gained more weight during pregnancy than did the COC users. The authors theorized that the relationship between POP use and increased diabetes risk may be due to a hypoestrogenic, progesterone-dominant metabolic environment in these lactating women. While estrogen does not impact glucose levels or insulin resistance, progesterone creates a relatively insulin-resistant environment. In COC users, this progesterone effect is dampened by the presence of the estrogen component, and glucose tolerance is maintained. Furthermore, the higher rates of glucose intolerance are unlikely attributable to lactation alone, since breastfeeding women using nonhormonal contraception are not at heightened risk of T2DM [94], and because data suggest that breastfeeding women with GDM have better glucose, insulin and lipids profiles

and possibly lower rates of T2DM, than do their non-breastfeeding counterparts [94,95].

A retrospective chart review reported the rates of subsequent diabetes in 592 women with GDM, followed for up to 24 months postpartum [93]. After 1 year, 36% of women who used progestin-only methods, compared with 23% of women who used nonhormonal methods, exhibited worsened glucose tolerance on 2-h oral glucose tolerance testing ( $p = 0.059$ ). In DMPA users, 43% had worsened glucose status after 1 year. In another study [92], investigators followed a cohort of 526 Latinas with prior GDM who used combined pills or DMPA for up to 9.2 years, finding an 1.58-times increased risk of subsequent T2DM in women using DMPA. The authors concluded that the increased risk of T2DM associated with DMPA use was explained by weight gain during use and use while breastfeeding.

Since contraceptive effectiveness depends on user compliance, LARC methods prevail as the most effective and reliable contraceptives. Implants and the levonorgestrel and copper IUDs offer highly effective contraception and low rates of infection and adverse events in both diabetic and nondiabetic users [96,97]. One randomized controlled trial [98] evaluated the metabolic effects of the levonorgestrel IUD in women with Type 1 DM. Sixty-two women with insulin-dependent DM were randomly assigned to either a copper or levonorgestrel IUD. Glycosylated hemoglobin levels, fasting glucose levels and daily insulin requirements were similar between groups after 6 weeks, 6 months and 12 months of use. No adverse effects on glycosylated hemoglobin, fasting glucose or insulin requirements were observed over time in either group. This trial provided evidence that the levonorgestrel IUD does not adversely affect glucose metabolism in Type 1 DM.

A recent Cochrane review [99] evaluated for differences between contraceptive methods in efficacy and metabolic effects in women with Type 1

**Table 3. Published studies on subsequent diabetes risk in women with gestational diabetes on contraceptives.**

Study (year)	Study type	Contraceptive types	Length of follow-up	Main findings	Ref.
Kjos <i>et al.</i> (1998)	Retrospective cohort	COC, POP, NH	Up to 7.5 years	Rate of T2DM for NH group = 8.7%, COC group = 10.4%, POP group = 26.5%. Adjusted relative risk 2.87 (95% CI: 1.57–5.27) for POP group compared with COC group. Higher rate of progression to T2DM in POP users who breastfed	[91]
Xiang <i>et al.</i> (2006)	Prospective cohort	COC, DMPA	Up to 9 years, median 12 months	Annual incidence of T2DM for DMPA group = 19%, COC group = 12%. Unadjusted hazard ratio 1.58 (95% CI: 1.00–2.50), adjusted hazard ratios not significant. DMPA use was associated with increased rate of T2DM, possibly explained by use in women with risk factors for DM, or by weight gain	[92]
Nelson <i>et al.</i> (2008)	Retrospective cohort	COC, POP, DMPA, NH	Up to 24 months	Worsened glucose tolerance in 23% of NH users, 21% of hormonal methods users, not significant DMPA users may have had higher rates of worsened glucose tolerance, with one or more dose, rate 43%. Not detected effect with lactation	[93]
Kiley <i>et al.</i> (2015)	Descriptive analysis	Progestin IUD, NH	12 months	Prediabetes diagnosed in 23.1% of progestin IUD users, 16.6% of NH users	[48]

COC: Combined oral contraceptive; DM: Diabetes mellitus; DMPA: Depot-medroxyprogesterone acetate; GDM: Gestational diabetes; NH: Non-hormonal contraceptives; POP: Progestin-only pill; T2DM: Type 2 diabetes mellitus.

and Type 2 DM. Three trials met inclusion criteria; two compared progestin-only and combined oral contraceptives, and the third was the previously mentioned randomized trial. The studies demonstrated no significant change in glycemic control, but reported effects of the oral preparations on lipid metabolism were mixed [100,101]. The review concluded that these trials provide insufficient evidence on the differential effects of hormonal and nonhormonal contraceptives on glucose and lipid metabolism in diabetic patients, and further studies are indicated.

While the need for reliable contraception in women with DM or previous GDM is recognized, the medical literature lacks evidence-based recommendations on the best contraceptive methods for women with a history of GDM. It remains unknown if the progestin released by the levonorgestrel IUD affects carbohydrate and lipid metabolism in users with DM. In addition, although one study [98] supports safety of levonorgestrel IUD use in Type 1 DM, women with GDM and T2DM are fundamentally different from those with Type 1. The incremental effect of insulin resistance in glucose intolerance and T2DM is more readily demonstrable and more clinically significant. In patients with GDM, an adverse effect on glucose metabolism manifests as decreasing glucose tolerance and increasing the risk of T2DM, with worsened hyperglycemia as a measurable outcome. The same degree of adverse effect in a patient with

Type 1 DM would be less clinically detectable, and even if detected would most likely not cause a significant clinical outcome. Only one published trial reports on glucose tolerance with IUD use in patients with GDM in a recent pregnancy. Nineteen women using levonorgestrel IUDs, copper IUDs or sterilization were followed through the first 12 months postpartum, and prediabetes was observed in 3 of 13 levonorgestrel IUD users and 1 of 6 nonhormonal method users [48].

Nonhormonal contraceptives do not impact glycemic control and are appropriate for women with GDM. The copper IUD is safe for use in women with glucose intolerance and diabetes [99], and should be considered as a first-line option in postpartum women with GDM. Sterilization should be considered for women who no longer desire fertility and choose a surgical procedure. The less reliable barrier contraceptives can be used by appropriate candidates who are compliant with coitally dependent methods.

### Conclusion & future perspective

Based on current evidence, women with past GDM are candidates for all hormonal and non-hormonal contraceptives, in the absence of other contraindications. As in all patients, recommendations for contraceptive use in these women should include consideration of medical comorbidities, plans for subsequent pregnancies, acceptability, convenience and noncontraceptive

benefits. Clinicians should consider LARC methods the first-line options in many women, based on their high effectiveness. However, the data on metabolic effects of hormonal contraceptives in women with GDM are incomplete, and the optimal contraceptive methods for women with GDM remain unclear.

The effect of lactation status on metabolism in women with GDM is unknown. Lactation offers many benefits, including improved postpartum weight loss and expedited return to pre-pregnancy weight. The interplay between hormonal contraceptives, lactation, and glucose and lipid metabolism is not well-defined. Future research should address this issue.

Postpartum contraception, LARC methods and contraception for women with chronic medical problems are high-priority topics for contemporary research. There is a need for well-designed studies on LARC and the appropriateness of hormonal contraceptives in women with medical risk factors. The prevalence of

GDM and the need for safe birth control in these women calls for scientific evaluation of the safety of progestin contraceptives in women with a history of GDM, who are at high risk for subsequent diabetes and its associated morbidity. In women whose pregnancy and future health outcomes are closely dependent on the timing of pregnancy – such as those with GDM who require optimal glycemic control – the benefits of finding the safest, most effective contraceptive types are paramount.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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