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Contraception for Women with Medical Problems

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INTRODUCTION

Women with medical problems often face greater obstacles in obtaining effective contraception based on their or their provider's belief that hormonal or intrauterine methods of contraception may place them at increased risk of infectious, metabolic, or vascular complications. Although research and educational efforts addressing contraceptive use in women with medical problems are limited, much of the current evidence in either healthy or diseased women does not support a significant increase in risk with use of most contraceptive methods. In fact, the alternative of pregnancy often poses a greater risk of morbidity or mortality in women with medical problems. Therefore, women should be offered the most effective methods of contraception that also preserve their existing health status.

In 2010, the World Health Organization (WHO) published the 4th edition of the Medical Eligibility Criteria for Contraceptive Use.[1] This document provides recommendations for the safety of various methods of contraception in women with certain health conditions. The conditions are classified from 1 to 4 for each type of contraceptive (see Table 1). Generally, methods classified as category 1 can be used without reservation while a category 2 classification signifies that the method can generally be used, but careful follow-up may be needed. Methods that are labeled category 3 require careful clinical judgment, and should generally not be used unless other more appropriate methods are unavailable or unacceptable. Finally, a category 4 designation indicates that the method is contraindicated in women with that condition.

Table 1. Meaning of category 1–4 recommendations in the WHO medical eligibility criteria (MEC) for contraceptive use. World Health Organization. Medical eligibility criteria for contraceptive use, 4th edition. Geneva, Switzerland; 2010

1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used

This chapter evaluates combined hormonal contraceptives (CHCs), including the combined oral contraceptive, transdermal patch, vaginal ring and injectable), progestin-based injectable and implanted hormonal methods, and the copper-bearing intrauterine devices (Cu-IUD) and levonorgestrel (LNG)-releasing intrauterine device (LNG-IUD) for use in women with various medical problems. Tier 3 (barrier and fertility awareness methods) and tier 4 (coitus interruptus and spermicides) contraception will not be addressed in this chapter because there are very few medical contraindications to their use, except for their higher failure rates. Medical conditions for which an unplanned pregnancy would pose significant health risk are listed in Table 2. Effective contraception is paramount for women with these conditions.

Table 2. Conditions associated with increased risk for adverse health events as a result of unintended pregnancy. Adapted from World Health Organization. Medical eligibility criteria for contraceptive use, 4th edition. Geneva, Switzerland; 2010

Breast cancer
Complicated valvular heart disease
Diabetes: insulin-dependent; with nephropathy/retinopathy/neuropathy or other vascular disease; or of >20 years' duration
Endometrial or ovarian cancer
Epilepsy
Hypertension
HIV/AIDS
Ischemic heart disease
Malignant gestational trophoblastic disease
Malignant liver tumors (hepatoma) and hepatocellular carcinoma of liver
Peripartum cardiomyopathy
Schistosomiasis with fibrosis of liver
Severe (decompensated) cirrhosis
Sickle cell disease
Solid organ transplantation within the past 2 years
Stroke
Systemic lupus erythematosus
Thrombogenic mutations
Tuberculosis

CARDIOVASCULAR DISEASE: HYPERTENSION

Women with chronic hypertension are at increased risk of poor obstetric outcomes, including superimposed preeclampsia, cesarean section, preterm delivery, and perinatal death.[2] Effective contraception is important in women with chronic hypertension to avoid unplanned pregnancy given these adverse pregnancy complications. However, contraceptive methods that worsen pre-existing hypertension should also be avoided to reduce risk of development of complications associated with chronic hypertension, including myocardial infarction, congestive heart failure, ischemic and hemorrhagic stroke, and renal disease.

Combination hormonal contraception

Combined oral contraceptives (COC) appear to increase blood pressure in users, even with current low dose regimens. One study demonstrated an average increase of 8 mmHg for systolic and 6 mmHg for diastolic blood pressures in 15 normotensive Caucasian women after 6–9 months of taking a COC containing 30 μg ethinyl estradiol/150 μg desogestrel, while women using an IUD had no increase in their blood pressures.[3] A cross-sectional study found that women using COC had higher diastolic blood pressures (100.2 ± 15.9 mmHg) compared to women using other (93.4 ± 14.7 mmHg) or no contraceptive method (93.3 ± 14.4 mmHg, $p = 0.016$). Additionally, after controlling for age, women who used COC for a longer duration (>8 years in this study) exhibited higher systolic and diastolic blood pressures than women who used COC for a shorter period of time.[4]

Even though the absolute increase in blood pressure reported is small, other studies have demonstrated an increase in cardiovascular disease in hypertensive women who use COCs. A systematic review published in 2006 reviewed the risks of myocardial infarction, hemorrhagic stroke, and ischemic stroke.[5] There were four case–control studies included that examined the risk of acute myocardial infarction with COC use.[6, 7, 8, 9] One of the studies, the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, reported the risk of acute myocardial infarction among women with hypertension using COCs. Among women living in Europe, hypertensive COC users had a significantly higher risk of myocardial infarction (OR 68.1, 95% CI: 6.18–751) compared to hypertensive non-users (OR 5.43, 95% CI: 2.39–12.4). Among women living in developing countries, hypertensive non-users continue to experience an elevated risk of acute myocardial infarction (OR 9.52, 95% CI: 4.90–18.5), and this risk increases tremendously among hypertensive COC users (OR 15.3, 95% CI: 3.27–71.6) compared to normotensive non-users.[6] A meta-analysis of COC use and risk of myocardial infarction with the four case–control studies demonstrated an increased risk of myocardial infarction in hypertensive women who use COCs (OR 9.30, 95% CI: 3.89–22.23).[10]

Stroke risk also appears to increase in hypertensive women who use COCs. Most studies demonstrate an increase in risk of 1.5 to 2 times for ischemic stroke among hypertensive women who use COCs compared to hypertensive non-users.[5] For example, an international case–control study found that European hypertensive women using COCs experienced a higher risk of ischemic stroke (OR 10.7, 95% CI: 2.04–56.6) compared to hypertensive non-users (OR 4.59, 95% CI: 2.39–8.82), with normotensive non-users as the reference group.[11] Similarly, the risk of hemorrhagic stroke was 1.5 to 2 times greater in hypertensive women who use COCs compared to hypertensive non-users. European hypertensive women who use COCs experienced a higher risk of hemorrhagic stroke (OR 10.3, 95% CI: 3.27–32.3) than hypertensive non-users (OR 4.94, 95% CI: 2.98–8.19) when compared to normotensive non-users as the reference group.[12] Among women living in developing countries, the odds ratio of hemorrhagic stroke in hypertensive COC users was 14.3 (95% CI: 6.72–30.4) and 9.41 (95% CI: 7.08–12.5) in hypertensive non-COC users.[12] Notably, despite the increase in risk, the incidence of myocardial infarction and stroke is low in reproductive-aged women, therefore the absolute risk is still low. For example, the risk of a cardiovascular event, specifically venous thromboembolism (VTE), ischemic and hemorrhagic stroke, and myocardial infarction, is 134, 241, and 529 per million woman-years in women aged 20–24, 30–34, and 40–44, respectively, who have hypertension but do not use COCs. Cardiovascular events increase nearly three-fold with the use of COCs by women with hypertension (312, 552, and 1213 per million woman-years in women aged 20–24, 30–34, and 40–44, respectively).[13]

Fortunately, women who discontinue COCs do experience a decrease in blood pressure. A prospective cohort study of 72 women who were instructed to stop COC due to hypertension found that participants who stopped taking COCs had a systolic blood pressure decrease of 15.1 ± 2.6 mmHg ($p = 0.004$) and diastolic blood pressure decrease of 10.4 ± 1.8 mmHg ($p = 0.008$) over 6 months of follow-up.[14]

Although there are other delivery systems of combined hormonal contraception, specifically the transdermal patch and vaginal ring, most of the studies examining combined hormonal methods only included oral contraceptive pills. A recent historical cohort study found that there was an increased risk of thrombotic stroke in vaginal ring users (RR 2.49, 95% CI: 1.41–4.41) but not in patch users (RR 3.15, 95% CI: 0.79–12.60). There was no increase in myocardial infarction risk in patch or vaginal ring users.[15] The authors did not examine the risk of patch or ring use in hypertensive women specifically. Given the limited data, recommendations for these other formulations are the same as for COC.

The risks of CHCs outweigh the benefit in women with a history of hypertension where blood pressure cannot be evaluated, adequately controlled hypertension, and elevated blood pressure (systolic 140–159 or diastolic 90–99 mmHg) (WHO MEC category 3). In women with severely elevated blood pressures (systolic ≥160 or diastolic ≥100 mmHg) or

evidence of vascular disease, CHCs represent an unacceptable health risk and should not be recommended (WHO MEC category 4).

Although it is preferred to have a blood pressure measurement before starting a woman on CHCs, if blood pressure cannot be evaluated in a woman with no history of hypertension (such as in a setting without medical personnel who know how to take a blood pressure measurement or without a working blood pressure cuff), the woman should not be denied estrogen containing methods. In such settings, pregnancy related morbidity and mortality are high and estrogen-containing pills may be one of the few contraceptive methods available.

Progestin-only methods

Three prospective studies evaluating the effect of progestin-only pills on development of hypertension in normotensive women found no changes in blood pressure over 24 months of follow-up.[16, 17, 18] A WHO multi-national case–control study evaluating the risk of cardiovascular disease with various contraceptive methods also demonstrated no increased risk of cardiovascular disease or stroke with progestin-only pills in normotensive women.[19] On the other hand, women with a history of hypertension who took progestin-only pills had an increased risk of composite cardiovascular disease events, specifically stroke, venous thromboembolism (VTE) and acute myocardial infarction (OR 7.58, 95% CI: 3.19–18.0), although this overlapped with the risk experienced by hypertensive nonusers (OR 5.87, 95% CI: 5.12–6.73). All stroke risk was increased in women with hypertension who did not use contraception (OR 7.21, 95% CI: 6.10–8.52) and in women using progestin-only pills (OR 12.4, 95% CI: 4.09–37.6).[19] Women with hypertension not using contraception had a 8-fold increase in risk of acute myocardial infarction (OR 8.05, 95% CI: 4.89–13.3) while hypertensive women taking progestin-only pills did not have any increased risk of acute myocardial infarction. The increased risk of cardiovascular disease and stroke is likely due to hypertension and it does not appear that progestin-only pills add significantly to this risk given the overlap in confidence intervals. Based on limited available evidence, there are no restrictions for use of progestin-only pills in women with adequately controlled hypertension or mildly elevated blood pressures (systolic 140–150 mmHg or diastolic 90–99 mmHg) (WHO MEC category 1). The benefits of progestin-only pills outweigh the risks in women with a history of hypertension where blood pressure cannot be evaluated, in women with severely elevated blood pressures (systolic ≥160 or diastolic ≥100 mmHg), and in women with vascular disease (WHO MEC category 2).

In the same WHO multinational case–control study, authors found that hypertensive women using depot medroxyprogesterone acetate (DMPA) experienced an increased risk of composite cardiovascular disease events (OR 7.16, 95% CI: 1.32–38.7), which also overlaps with the risk experienced by hypertensive non-users (OR 5.87, 95% CI: 5.12–6.73).[19] No other study has evaluated the risk of cardiovascular events with DMPA in hypertensive women. In women with a history of hypertension, adequately controlled hypertension, and mildly elevated blood pressures, the benefits of DMPA outweigh the risks (WHO MEC category 2). However, the risks outweigh the benefits in women with severely elevated blood pressures and vascular disease (WHO MEC category 3).

Intrauterine devices

There are no studies evaluating the effect of the Cu-IUD and LNG-IUD on hypertension. However, there are no known effects of the Cu-IUD on hypertension. Accordingly, there are no restrictions for use in women with hypertension (WHO MEC category 1). Similarly, there are no restrictions for LNG-IUD use in women with adequately controlled hypertension and mildly elevated blood pressures (WHO MEC category 1). The benefits of LNG-IUD outweigh the risks in women with a history of hypertension, severely elevated blood pressures, and vascular disease (WHO MEC category 2).

ENDOCRINE DISORDERS: DIABETES

Diabetes mellitus (DM) is characterized by abnormal carbohydrate metabolism due to absolute or relative lack of insulin leading to hyperglycemia. End-organ damage generally occurs with prolonged disease, including microvascular disease (retinopathy, peripheral neuropathy, and nephropathy) and macrovascular disease (coronary vascular disease). Women with poorly controlled DM are at increased risk of adverse pregnancy outcomes, including congenital malformations, macrosomia, preeclampsia, cesarean delivery, spontaneous abortions and intrauterine fetal demise. The presence and increasing severity of diabetic vascular sequelae influence the patient's prognosis, quality of life, and risk of pregnancy complications. Similarly, the presence of vascular disease affects contraceptive choices.

Combined hormonal contraception

CHCs have traditionally been thought to adversely affect carbohydrate metabolism by increasing insulin resistance and decreasing glucose tolerance. However, low dose COCs do not seem to cause any clinically important changes in carbohydrate metabolism. A retrospective case–control study of women with type 1 DM found no difference in HbA1c levels in women who had used COCs for 1–7 years compared to non-users.[20] In addition, a prospective study of 153 women with both type 1 and type 2 DM without any evidence of proliferative retinopathy, nephropathy or macrovascular complications were randomized to receive 20 μg ethinyl estradiol/150 μg desogestrel, 30 μg ethinyl estradiol/150 μg desogestrel, 30 μg ethinyl estradiol/75 μg gestodene, Cu-IUD, LNG-IUD or no contraceptive method. Over a 1-year period, authors did not find a significant difference in HbA1c among women in the control and treatments group.[21] Another open randomized study compared the use of the vaginal ring in 25 women with type 1 DM, 20 women with type 1 DM not using contraception and 20 healthy women. Again, there were no significant differences in HbA1c level over 6 months among the control and treatment groups. Furthermore, there was no difference in clinical manifestations of microvascular complications.[22]

Findings in studies utilizing other measures of diabetic control in women taking COCs have been mixed; some studies found an increase in insulin requirements[21] and fasting glucose levels,[23] while others demonstrated no change in glycemic control or lipid profiles.[24, 25] In regards to the risk of developing long-term microvascular and macrovascular complications in women with DM who use COCs, an observational cohort study including 484 participants found that reported COC use had no significant association with the severity of retinopathy compared to non-use over 4 years follow-up after controlling for confounding factors, such as disease duration, blood pressure, HbA1c levels, proteinuria and body mass index.[26] Another cohort study reported no association between COC use and cardiovascular mortality in women with DM after 12 years of follow-up.[27]

Overall, in women with DM without vascular disease, the advantages of using CHCs outweigh the risks (WHO MEC category 2). On the other hand, limited data exist on the risk of CHC use in women with vascular complications of DM. Therefore, women with vascular complications (nephropathy, retinopathy, and neuropathy) and women with diabetes of greater than 20 years' duration should avoid CHC use unless no other methods are available (WHO MEC category 3 or 4 depending on severity of the condition).

Progestin-only methods

Few studies evaluated the use of progestin-only methods of contraception in women with DM. Two studies compared progestin-only pills with other contraceptive methods. Radberg *et al.*[28] compared 0.5 mg lynestrenol with a COC containing 50 μg ethinyl estradiol/2.5 mg lynestrenol in 23 diabetic women using a crossover design. Although women taking 0.5 mg lynestrenol had significant increases in urinary glucose, there was no change in blood glucose or daily insulin dosage. Furthermore, serum cholesterol, phospholipids, and triglycerides decreased after taking 0.5 mg lynestrenol.[28] A second study compared 300 μg norethindrone with three other COC formulations in 27 women over a period of 6 months. There were no significant differences in fasting glucose level, HbA1c level, or insulin requirements

among all groups.[25] Based on these studies, it appears that progestin-only pills have limited effect on glycemic control and lipid profiles and can be used in diabetic women with both non-vascular disease and vascular disease (WHO MEC category 2).

Diab *et al*.[23] followed 80 diabetic women without evidence of vascular complications who chose Cu-IUD, LNG implant, DMPA or 30 μg ethinyl estradiol/75 μg gestodene COC over 9 months. The authors found that diabetic women using depot medroxyprogesterone acetate (DMPA) had increases in fasting glucose levels, total cholesterol and low-density lipoprotein cholesterol as well as decreases in high-density lipoprotein cholesterol. Diabetic women in the LNG implant group experienced decreases in total cholesterol and high-density lipoprotein cholesterol. Despite these changes in serum glucose values and lipid parameters, there were no significant changes in insulin or oral treatment doses among all groups.[23] A recent prospective observational study evaluating the effect of the etonogestrel implant on glycemic control and lipid profiles in women with DM over 24 months found no differences in daily insulin requirements and HbA1c levels. Authors also found significant decreases in serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol over 24 months.[29] Given these findings, the benefits of LNG or etonogestrel implant outweigh the risks for use in women with DM, both with and without vascular complications (WHO MEC category 2). Conversely, limited evidence indicates that DMPA is associated with adverse changes in carbohydrate and lipid metabolism. Therefore, in diabetic women without vascular complications, the benefit of DMPA use outweighs the risks (WHO MEC category 2); however, in women with vascular complications or who have had the disease for over 20 years, the risks of use outweigh the benefits (WHO MEC category 3) based on theoretical increased cardiovascular risks in these women if using DMPA.

Intrauterine devices

The Cu-IUD has been shown to be safe for use in women with DM. In a study examining the use of the Cu-IUD in 103 women with type 1 DM and 119 healthy women over 1 year, no pelvic infections or perforations occurred, and the incidence of failure, expulsion, and pain was similar in the two groups.[30] In another 3-year trial involving 59 women with type 1 DM and 1043 women without diabetes using the Cu-IUD, no cases of pelvic inflammatory disease were found after 1754 cumulative months of use in the diabetic cohort.[31] Accordingly, there are no restrictions for use of the Cu-IUD in diabetic women with and without evidence of vascular disease (WHO MEC category 1).

Limited data exist on the use of the LNG-IUD in women with DM. In a previously described study on women with DM treated with different formulations of COCs, Cu-IUD, and LNG-IUD, there were no differences in HbA1c levels or lipid profiles in LNG-IUD users compared with healthy controls.[21] A randomized controlled trial comparing Cu-IUD with LNG-IUD in insulin-dependent diabetic women without microvascular complications demonstrated no difference in HbA1c levels, fasting glucose, and daily insulin requirements over 12 months.[32] These studies suggest that the benefits of LNG-IUD outweigh any potential risks in diabetic women with and without vascular disease (WHO MEC category 2).

RHEUMATIC DISORDERS: SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that disproportionately affects women of reproductive age. SLE can affect multiple organ systems, including the skin, joints, kidney, lung, and blood. SLE has a variable course, which is characterized by exacerbations and remissions. The risk of a lupus flare during pregnancy depends on disease activity in the preceding 6–12 months. Furthermore, women with active disease are at increased risk of obstetric complications, including preterm delivery, preeclampsia, intrauterine growth restriction, and stillbirth.[33] Accordingly, women should ideally achieve pregnancy during a period of disease quiescence.

Many women with SLE can be considered good candidates for most contraceptive methods, including hormonal contraception.[34, 35] However, it is important to note that there is increased risk of ischemic heart disease, stroke, and VTE in women with SLE.[36, 37] Therefore, women with SLE and one of these co-existing conditions should receive the same

recommendations as other women with these conditions. The WHO guidelines are divided into four sub-categories based on evidence of differing risks for different complications of the disease. The sub-categories are: positive (or unknown) antiphospholipid antibodies, severe thrombocytopenia, immunosuppressive treatment, and none of these risk factors.

Combined hormonal contraception

Historically, due to concerns about increasing disease activity in women with SLE, most practitioners have avoided prescribing CHCs for these women. However, two recent randomized controlled trials found no increased risk of disease flares in women with inactive or stable SLE when taking combined oral contraceptives. Sanchez-Guerrero *et al.* conducted a single-blind trial that included 162 women: 54 received 30 μg ethinyl estradiol/150 μg levonorgestrel, 54 took 30 μg levonorgestrel, and 54 had the TCu380A IUD placed.[38] There was no difference in global disease activity over 1 year as measured by the Systemic Lupus Erythematosus Disease Activity Index among the three groups. In Petri and colleagues' multicenter, double-blind, placebo-controlled trial, 183 women were randomized to receive 35 μg ethinyl estradiol triphasic COC or identical placebo.[39] The flare rate was similar between two groups over 1 year. Based on these studies, the benefits of CHC use outweigh the risks in women with mild and stable disease (WHO MEC category 2) and without the above mentioned risk factors.

Women with antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibody, anti beta 2 glycoprotein, are at increased risk of both arterial and venous thrombosis.[40, 41] Therefore, they are not candidates for CHCs (WHO MEC category 4).

Progestin-only methods

In general, progestins do not induce changes in coagulation factors that would increase the risk of thrombosis.[42] However, previous studies demonstrate a possible association of increased VTE risk with progestin-only methods. For example, in the WHO collaborative study of cardiovascular disease and steroid hormone contraception multicenter case–control study, there was a slight, non-significant increase in VTE risk in oral (OR 1.74, 95% CI: 0.76–3.99) and injectable progestin users (OR 2.19, 95% CI: 0.66–7.26).[19] Bergendal *et al.*'s meta-analysis also revealed a slight, but non-significant risk of VTE with progestin-only contraceptives (OR 1.45, 95% CI: 0.92–2.26).[43] Given the possible increased risk of thromboembolism with progestin-based contraceptives, women with SLE and antiphospholipid antibodies, who are at the highest risk of VTE, should use these methods with caution (WHO MEC category 3).

Severe thrombocytopenia increases the risk of bleeding, and women with this disorder can often experience heavy menstrual bleeding. All progestin-based contraceptives are acceptable for use (WHO MEC category 2) except for DMPA initiation given the potential for irregular bleeding with this method and exacerbation of bleeding in the short term upon initiation in the context of thrombocytopenia (WHO MEC category 3).

Intrauterine devices

Although there are limited data regarding the use of IUDs in women with SLE, IUDs are generally safe in women who desire effective contraception.[44] There are no restrictions for use of the Cu-IUD in women with antiphospholipid antibodies (WHO MEC category 1). Women with severe thrombocytopenia should exercise caution with consideration to the Cu-IUD given the potential for increased bleeding. On the other hand, the LNG-IUD can be used to treat heavy menstrual bleeding related to thrombocytopenia. However, women with very severe thrombocytopenia are at risk of spontaneous bleeding and should consult with a specialist and potentially undergo certain pre-treatments before insertion of the IUD.

Women who take immunosuppressive therapy or have no SLE-related complications are eligible for all contraceptive methods, as the benefits generally outweigh the risks (WHO MEC categories 1 and 2). Women and their providers may be concerned about the risk of infection with IUD insertion in the setting of immunosuppression. It is reassuring that studies in women with other types of immunosuppression, such as HIV, have not shown an increased risk of pelvic infection with IUD use.[45, 46] Minimal evidence in women with SLE shows no increased risk of infection with use of the IUD.[38, 47]

HEMATOLOGIC DISORDERS: SICKLE CELL DISEASE

Sickle cell disease (SCD) is an autosomal recessive disorder that produces an abnormal hemoglobin tetramer that assumes a "sickle" shape when deoxygenated. The polymerization of these sickled red blood cells renders the cells unable to traverse the microcirculation, resulting in obstruction, thrombosis, and tissue infarction. These fragile red blood cells are also more prone to breakage, leading to anemia. Clinically, SCD is characterized by vaso-occlusive pain crises, anemia, and long-term organ complications.

Women with SCD are at increased risk of obstetric complications, such as intrauterine fetal demise, intrauterine growth restriction, preterm birth, hypertensive disorders, cesarean section, and even maternal mortality.[48, 49] The frequency of pain crises also increases for some women during pregnancy.[50] Accordingly, appropriate contraception is critical to decrease unintended pregnancy in these women.

Combined hormonal contraceptives

Women with SCD are at increased risk of VTE, likely resulting from a chronically activated coagulation system.[51] Given the increased baseline risk of VTE in women with SCD, there is concern that introducing CHCs can further increase the risk of VTE. Limited studies, however, indicate that CHCs can be safely used in women with SCD. In de Abood *et al.*'s non-randomized trial of women taking a COC containing 30 µg ethinyl estradiol/150 µg levonorgestrel, women experienced less pain episodes, decreasing from 100% of participants at the start of the trial to 45.5% of participants reporting painful crises after 1 year.[52] Findings from two cross-sectional studies demonstrated no significant differences in hematologic markers of platelet activation, thrombin generation, fibrinolysis and red cell deformability among women with SCD using CHCs, progestin-only methods and non hormonal contraception.[53, 54] Despite the theoretical increased risk of VTE in women with SCD, it is important to note that pregnancy poses an even greater risk of VTE for women with this condition. A population-based retrospective cohort study found that women with SCD conditions (hemoglobin SS, hemoglobin SC, or hemoglobin S/B-thal) had a higher risk of VTE (RR 54, 95% CI: 12–253) during pregnancy when compared to women with normal hemoglobin.[55] Although the number of VTE cases was low in this study, the findings do reinforce that the risks associated with an unplanned pregnancy in a woman with SCD far outweigh the risks of contraception. In summary, CHCs are WHO MEC category 2 for women with SCD.

Progestin-only methods

Two systematic reviews examined the use of progestin-based contraception in women with SCD and found that women often experienced an improvement in symptoms with these methods.[56, 57] De Abood *et al.*'s study also included women who received DMPA and found that these women experienced a decrease in painful crises from 100% with at least one painful crises per month to only 30% reporting regular sickle cell crises at 1 year.[52] In another study by De Ceulaer and colleagues, 23 women received either DMPA (150 mg every 3 months for 3 cycles) or placebo in a blinded, crossover trial with a 6-month washout between study injections.[58] During the treatment phase with DMPA, there were significant increases in the levels of fetal and total hemoglobin and the count, mass, and survival of red cells; decreases in reticulocyte and irreversible sickled cell counts, serum total bilirubin, and in number of episodes of bone pain compared with the placebo periods. Overall, there are no restrictions to the use of progestin-only methods in women with SCD (WHO MEC category 1).

Intrauterine devices

Limited data exist on IUD use in women with SCD. There is one cross-sectional study examining the experience of women with SCD with different contraceptive methods, including COCs, progestin-only pill, IUD (type not specified), and DMPA. The 28 women who used IUD in this study reported side-effects of dysmenorrhea (28.6%), menorrhagia (39%), infection (17.9%), and increased crises (3.57%).[59] However, no one discontinued this method as a result of side-effects. Furthermore, there were no comparative statistics performed to compare the side-effects of IUD with other methods, limiting the ability to comment on the safety profile based on this study. Therefore, the WHO has given the Cu-IUD a WHO MEC category 2 classification due to the theoretical concern of an increased risk of blood loss. There are no restrictions for use of the LNG-IUD (WHO MEC category 1).

HEMATOLOGIC DISORDERS: THROMBOGENIC MUTATIONS

Several gene mutations are associated with an increased risk of thrombosis, including mutations in factor V Leiden and prothrombin, and deficiencies in protein S, protein C, and antithrombin.[60] Pregnancy and the postpartum state confer a high risk of VTE in women with inherited thrombophilias;[61] therefore, safe and effective contraception is critical in this group.

Combined hormonal contraceptives

The baseline risk of VTE in healthy women is 0.8 per 10,000 person-years. Although COC use increases the risk of VTE by about three to six-fold, this would be an absolute risk of VTE of 3–4 per 10,000 person years.[62] In otherwise healthy women, this risk is much less than the risk of VTE in pregnancy and postpartum. The incidence of thromboembolism during the postpartum period is up to five times higher than during pregnancy and 22- to 84-fold higher than in non-pregnant women.[63, 64] In women with thrombogenic mutations, however, the VTE risk substantially increases. One of the initial studies demonstrated that the risk of VTE goes up eight-fold in women with factor V Leiden mutation not using COCs (OR 7.9, 95% CI: 3.2–19.4) and increases more than 30-fold in women with factor V Leiden mutation taking COCs (OR 34.7, 95% CI: 7.8–154).[65] Subsequent studies have also shown an elevated risk of VTE in women with thrombophilia using COCs, with a wide range of risk estimates from 3 to 80-fold higher.[66, 67, 68, 69, 70, 71] A meta-analysis examining the risk of COC use in women with thrombogenic mutations demonstrated a 14-fold higher risk of thrombosis in women with thrombophilia compared to women without thrombophilia and not using COCs (OR 14.1, 95% CI: 6.27–31.72).[72] Given these risks, the use of CHCs in women with thrombogenic mutations is contraindicated (WHO MEC category 4).

Furthermore, the issue of screening women for inherited thrombophilias prior to starting CHCs has been raised. However, a cost-effectiveness analysis of screening for factor V Leiden mutation in the United States, where the prevalence of factor V Leiden is higher than other thrombogenic mutations, found that a cohort of >90,000 women who have factor V Leiden would need to be identified and stopped from COC use to prevent one death caused of VTE. The estimated costs of such a screening program exceed $300 million, rendering screening for thrombophilias not cost-effective.[73]

Progestin-only methods

While it is certain that progestin-only methods do not carry the same risk of thromboembolism as do methods containing estrogen, whether there is no risk or simply a lower risk of thromboembolism with progestin-only methods is not as clear. The use of progestin-based contraception has not been shown to confer an increased risk of VTE in several large observational studies.[19, 74, 75, 76] A recent meta-analysis of eight observational trials found no increased risk of

thromboembolism with use of progesterone-only pills or the LNG-IUD, but that there may be an increased risk with progestin-only injectables.[77] Based on the best available evidence, progestin-only methods are considered acceptable for use in women with thrombogenic mutations (WHO MEC category 2).

Progestin-only contraceptives have also been used in the setting of anticoagulation for management of gynecologic bleeding. For example, Sonmezer *et al.*[78] reported the outcomes of 13 women with prosthetic heart valves on chronic anticoagulation with warfarin who were hospitalized for hemorrhagic ovarian cysts. Prior to discharge, these women received DMPA to prevent ovulation and were followed prospectively for an average of 39.9 months. In the follow-up period, no further hemorrhagic ovarian cysts were seen. In women with VTE and on anticoagulant therapy, the use of progestin-only contraception is acceptable (WHO MEC category 2).

Intrauterine devices

Limited studies suggest that the LNG-IUD is not associated with an increased VTE risk. For example, in a recent historical national registry based cohort study, the adjusted relative risk of VTE in LNG-IUD users was 0.57 (95% CI: 0.41–0.81).[79] Similar findings are seen in previous studies.[80, 81] As a result, the LNG-IUD is acceptable for use in women with thrombogenic mutations (WHO MEC category 2).

The LNG-IUD has also been studied for management of bleeding in women on anticoagulation.[82] Most of these studies have small sample sizes and include women with various hematologic disorders, such as von Willebrand's disease, immune thrombocytopenia, or a history of thromboembolic disorder on anticoagulation.[83, 84, 85] Despite the small numbers, the study findings suggest that the LNG-IUD is an effective method to decrease heavy menstrual bleeding in women with hemostatic disorders. For example, in a survey study by Pisoni *et al.*,[86] 58% of women taking oral anticoagulation for a history of thrombosis reported a decrease in bleeding with the LNG-IUD and 71% reported being satisfied or very satisfied with the method. Accordingly, the LNG-IUD is acceptable for use in women with VTE on anticoagulation therapy (WHO MEC category 2).

The use of a Cu-IUD is not associated with an increased risk of VTE; therefore, there are no restrictions for use in women with thrombophilia (WHO MEC category 1) and in women with VTE on anticoagulation therapy (WHO MEC category 1). However, consideration should be given to women on anticoagulation therapy who develop menorrhagia as a consequence of anticoagulation before insertion of the Cu-IUD, which may increase menstrual flow in the months following insertion.

INFECTIOUS DISEASES: HIV

Heterosexual intercourse is a leading mode of transmission for human immunodeficiency virus (HIV) worldwide. The correct and consistent use of condoms decreases the risk of HIV transmission among serodiscordant couples,[87] and dual protection against HIV transmission and pregnancy is achieved with condoms and another form of contraception. Effective contraception is important in women with HIV to decrease unintended pregnancy and risk of vertical transmission of HIV. In terms of non-barrier methods of contraception, the choice of contraceptive method depends on its effect on HIV transmission, potential impact on disease progression, and drug interactions. Antiretroviral medications fall into six main categories: nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), CCR5 antagonists, and fusion inhibitors.

Combined hormonal contraceptives

WOMEN AT HIGH RISK OF HIV

The use of COCs does not appear to increase the risk of HIV acquisition and transmission.[88] In a study of women in sub-Saharan Africa, the use of COCs was not associated with HIV acquisition (HR 0.86, 95% CI: 0.32–1.78).[89] In another study of serodiscordant couples, the adjusted OR was 1.59 (95% CI: 0.32–97.85) for female conversion to HIV with COC use and adjusted OR of 2.11 (95% CI: 0.18–25.26) for male conversion to HIV with female partner COC use.[90] Based on the available evidence, there is no restriction for CHC use in women at risk of HIV (WHO MEC category 1).

WOMEN WITH HIV

In terms of the effect of hormonal contraception on disease progression, study findings indicate that COCs do not hasten disease progression in women with HIV, which is typically defined as time to initiation of combination antiretroviral therapy, CD4 count less than 200 cells/ml, or death not due to trauma.[91] For example, a recent prospective study of 2269 African women with HIV over 3242 years of follow-up found that women using COCs did not have increased rates of disease progression compared to women not using contraception (hazard ratio 0.83, 95% CI: 0.48–1.44).[92] There is no restriction for CHC use in women with HIV, WHO clinical stages 1–4 (WHO MEC category 1).

WOMEN TAKING ANTIRETROVIRAL THERAPY

Steroid hormones are metabolized by the hepatic cytochrome p450 enzyme system, especially by the 3A4 isoenzyme. Drug interactions with hormonal contraception may occur with antiviral medications that induce or inhibit the cytochrome p450 enzyme. NRTIs are not metabolized by cytochrome p450 enzymes, and pharmokinetic studies show that steroid hormone levels are not affected by NRTIs.[93] For example, tenofovir, a commonly used antiretroviral, was administered with triphasic norgestimate (0.18/0.215/0.25 mg) and 35 μg ethinyl estradiol COC in 20 healthy women. The pharmacokinetic values of norgestimate and ethinyl estradiol were the same with and without tenofovir.[94] Similar findings were seen with COCs and zidovudine.[95] There are no restrictions for CHC use in women taking NRTIs (WHO MEC category 1).

On the other hand, NNRTIs can inhibit or induce the cytochrome p450 enzyme. A study published in 2002 that used a COC containing 35 μg of ethinyl estradiol/1 mg norethindrone and multi-drug antiretroviral regimens that included nevirapine showed that there was a significant median reduction of 29% in the AUC of ethinyl estradiol after administration of nevirapine (p = 0.014) and a significant median reduction of 18% in norethindrone after taking nevirapine (p = 0.016). This study was limited by a small sample size of 10 participants, and pharmacokinetic data were not normally distributed.[96] A more recent non-randomized prospective clinical trial with a larger sample size (196 women taking nevirapine-based antiretroviral regimen and 206 women not yet taking antiretroviral therapy) found that antiretroviral use had no association with ovulation (OR 1.47, 95% CI: 0.85–2.55), as determined by serum progesterone levels. This study concluded that nevirapine-containing antiretroviral regimens did not affect COC effectiveness.[97] The benefits of CHCs outweigh the risks in women taking nevirapine antiretroviral therapy (WHO MEC category 2).

A prospective, open-label, non-randomized steady-state clinical trial evaluated the interactions between nevirapine or efavirenz and a COC that contained 30 μg ethinyl estradiol/150 μg desogestrel. All 18 women in the nevirapine group had serum progesterone levels <1.0 ng/mL, indicating that ovulation did not occur. Furthermore, the median concentration of nevirapine did not change significantly with addition of COC. On the other hand, three of 16 subjects had serum progesterone levels >3.0 ng/mL, suggesting that ovulation might have occurred. The median concentration of efavirenz was also significantly decreased after addition of COC (p = 0.03).[98] With limited data, the benefits of CHCs outweigh the risks in women taking efavirenz antiretroviral therapy (WHO MEC category 2).

Studies also demonstrate COC pharmacokinetics are not impacted by two other NNRTIs, rilpirivirine[99] and etravirine.[100] There are currently no restrictions for use of CHCs in women taking these two antiretrovirals (WHO MEC category 1).

Conversely, protease inhibitors, appear to decrease steroid hormone concentrations when co-administered with CHCs. One study examined women who took either a COC containing 35 μg ethinyl estradiol/1 mg norethindrone or the transdermal contraceptive patch, with or without lopinavir/ritonavir. Authors found that median patch ethinyl estradiol concentrations were lower in the women who were taking lopinavor/ritonavir (p = 0.064) while median patch norelgestromin concentrations were higher in women treated with lopinavir/ritonavir (p = 0.036). In COC users, median concentrations of ethinyl estradiol were lower in women taking lopinavir/ritonavir.[101] Overall, the benefits of CHC use appear to outweigh the risks in women taking protease inhibitors (WHO MEC category 2). However, the WHO cautions that antiretroviral drugs have the potential to either increase or decrease steroid hormone levels and that these interactions may potentially decrease contraceptive efficacy.

Raltegravir, an integrase inhibitor, appears to have no clinically significant effects on the pharmacokinetic profiles of ethinyl estradiol or norelgestromin in women taking both raltegravir and Ortho Tri-Cyclen (norgestimate-ethinyl estradiol).[102] CHCs have no restrictions for use in women taking raltegravir (WHO MEC category 1).

Progestin-based methods

WOMEN AT HIGH RISK OF HIV

The influence of progestin-based methods, specifically DMPA, on HIV acquisition is unclear. Studies in rhesus macaques show that administration of progesterone causes thinning of the cervicovaginal epithelium, potentially explaining the increased susceptibility to HIV acquisition among DMPA-treated macaques.[103] Despite biologic plausibility demonstrated in animal studies, epidemiologic study findings are mixed. Several studies have found a 1.5–2 times increased risk of HIV acquisition among women using DMPA for contraception[104, 105, 106] while other studies indicate no increased risk.[107, 108, 109, 110, 111] Because of the inconclusive results, WHO recommends no restrictions to the use of progestin-based methods in women at high risk of HIV (WHO MEC category 1); however, consistent condom use should be practised to minimize risk of HIV acquisition.

WOMEN WITH HIV

A trial examining the effect of hormonal contraception on HIV progression randomized 599 postpartum Zambian women to either the Cu-IUD or hormonal contraception (DMPA or COC) and followed these women for at least 2 years.[46] Disease progression was defined as death, CD4 count falling to less than 200, or either of these outcomes. This study was notable for high rates of study withdrawal (13%), lost to follow-up (15%), and method discontinuation (13% in the hormonal contraception group and 49% in the IUD group). Nonetheless, initial study results found an increased risk of CD4 count falling to less than 200 in hormonal contraception versus IUD users (HR 1.6, 95% CI: 1.04–2.3).[46] A secondary analysis of this study's results sought to determine whether DMPA specifically, hastened HIV disease progression.[112] Given the high method discontinuation rates, both intention-to-treat (ITT) and actual-use analyses were performed. There was no difference in mortality rates among the groups. However, in both the intention-to-treat and actual-use analyses, there was an increased risk of CD4 count falling to less than 200 or need to start antiretroviral therapy in DMPA users (ITT HR 1.81, 95% CI: 1.26–2.6; actual-use HR 1.56, 95% CI: 1.08–2.26).[112]

Cohort studies do not report the same findings as the randomized trial above. A recent prospective cohort study of 2269 HIV positive women contributing 3242 person-years of follow-up found that users of DMPA experienced lower rates of disease progression compared to women not using hormonal contraception (8.39 versus 12.31 per 100 person-years, p = 0.04).[92] A systematic review of the evidence also concluded that hormonal contraception does not appear to hasten disease progression in HIV positive women.[91] Based on available evidence, progestin-based methods have no restriction for use in women with HIV of all clinical stages (WHO MEC category 1).

WOMEN TAKING ANTIRETROVIRAL THERAPY

An open-label pharmacokinetic study examined the use of DMPA in 70 subjects taking an NRTI or no antiretroviral therapy (control arm) compared with NRTI and nelfinavir, efavirenz, or nevirapine. There were no changes in AUC 0–12 weeks for DMPA and serum progesterone levels among the various groups. There was no difference in drug exposure after DMPA in women taking nelfinavir and efavirenz, whereas drug exposure to nevirapine was slightly increased 4 weeks after DMPA use.[113] Another open-label pharmacokinetic study evaluated the effect of a common antiretroviral therapy (zidovudine, lamivudine, and efavirenz) on DMPA pharmacokinetics. In both the antiretroviral and non-antiretroviral group, the mean AUC, mean max plasma MPA concentrations, and median time to maximum MPA levels were similar.[114] Overall, there are no restrictions for DMPA use in women with HIV taking NRTIs, NNRTIs, PI, or integrase inhibitors (WHO MEC category 1).

There are several case reports of etonogestrel implant failure in women on antiretroviral therapy, specifically zidovudine, lamivudine, and efavirenz[115, 116, 117] and tenofovir/emtricitabine and efavirenz.[117] Efavirenz, a NNRTI, is a cytochrome P450 enzyme inducer, and co-administration of NNRTI with steroidal hormones may result in contraceptive failure due to a decrease in steroidal hormonal levels. Recent pharmacokinetic studies demonstrate a decrease in bioavailability of etonogestrel in women taking efavirenz. One study included 14 women taking zidovudine/lamivudine and lopinavir/ritonavir, 14 women treated with zidovudine/lamivudine and efavirenz, and 14 HIV-positive women not being treated with antiretroviral therapy, all of whom selected the etonogestrel implant as a method of contraception. The mean AUC 0–24 weeks of etonogestrel in the lopinavir/ritonavir-based group was 52% higher compared to the non-therapy group (p <0.01), whereas the mean AUC 0–24 weeks of etonogestrel in the efavirenz-based group was 63.4% lower than the non-therapy group (p <0.01).[118] The use of etonorgestrel implant in women taking NRTIs is unrestricted (WHO MEC Category 1). Although the benefits of etonorgestrel implant outweigh the risks in women taking efavirenz or nevirapine (NNRTIs), caution should be exercised in light of recent study findings (WHO MEC Category 2). In contrast to NNRTIs, ritonavir inhibits cytochrome P450, increasing the bioavailability of etonogestrel. Despite this drug interaction, contraceptive efficacy of the etonorgestrel implant should not be affected, and the recommendations are that the benefits outweigh the risks of use (WHO MEC category 2).

Intrauterine devices

WOMEN AT HIGH RISK OF HIV

A review of several studies, including three prospective trials, indicates that the Cu-IUD does not appear to increase the risk of HIV acquisition.[119] A recent trial examining genital tract immune cell populations of women randomized to Cu-IUD or LNG-IUD found that the percentage of cervical CD4 T lymphocytes expressing CCR5, a target coreceptor for HIV transmission, was reduced after placement of LNG-IUD (54% to 38%, p <0.05) and Cu-IUD (55% to 35%, p <0.01) over a 2-month period. CCR5 expression also decreased in endometrial T cells in both Cu-IUD and LNG-IUD users.[120] These findings suggest that susceptibility to HIV acquisition, as determined by genital tract immune cells, is not increased with both types of IUD use. Currently, the advantages of using the Cu-IUD outweigh the risks (WHO MEC Category 2), and there are no restrictions for use of the LNG-IUD in women at high risk of HIV (WHO MEC category 1).

WOMEN WITH HIV

Previously, IUDs have not been recommended for use in women with HIV due to theoretical concerns about an increased risk of infection and viral shedding. However, studies have shown that the Cu-IUD is not associated with increased complications in women with HIV. In Sinei *et al.*'s study, 144 Kenyan women with HIV did not experience an increased composite complication rate (pelvic inflammatory disease, IUD removals, IUD expulsions, and pregnancies) compared to women without HIV (adjusted odds ratio 0.80, 95% CI: 0.38–1.68) at 1 and 4 months after IUD insertion.[121] Another study evaluating cervical shedding of HIV-1 DNA found no difference in prevalence of shedding before and after IUD insertion (OR 0.6, 95% CI: 0.3–1.1). The only variable found to be associated with shedding prevalence was CD4 count;

specifically, an increase in CD4 cell count was associated with a decrease in odds of cervical shedding of HIV-1 DNA.[122] Similarly, limited studies indicate that the LNG-IUD is safe for use among women with HIV. In one study of 15 women over a 5-year follow-up period, LNG-IUD use was not associated with changes in CD4 count or need to start antiretroviral therapy compared non-use of LNG-IUD.[123] Another study of HIV-1 infected women in Kenya demonstrated no change in endocervical or cervicovaginal HIV-1 RNA before and 6 months after LNG-IUD placement.[124] In light of these studies, the advantages of initiating or continuing the Cu-IUD outweigh the risks (WHO MEC category 2). In women with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2), the advantages of initiating or continuing the LNG-IUD outweigh the risks (WHO MEC category 2). However, in women with severe or advanced HIV clinical disease (WHO stage 3 or 4), the risks of LNG-IUD initiation outweigh the benefits (WHO MEC category 3), whereas the benefits of continuing the LNG-IUD outweigh the risks (WHO MEC category 2).

WOMEN TAKING ANTIRETROVIRAL THERAPY

One of the earliest studies examining the use of LNG-IUD in women with HIV demonstrated no differences in serum LNG levels between women taking and not taking antiretroviral therapy in a group of 12 participants,[125] suggesting that there are no drug interactions between the LNG-IUD and antiretroviral therapy. Similarly, there are no known drug interactions between Cu-IUD and antiretroviral therapy. Subsequently, the recommendations for IUD use follow those for women with HIV. In women with WHO clinical stages 1 and 2, the benefits of initiation or continuation of LNG-IUD and Cu-IUD outweigh the risks (WHO MEC category 2), whereas for women with advanced or severe disease (WHO clinical stages 3 and 4), caution should be exercised with LNG-IUD and Cu-IUD initiation (WHO MEC category 3).

NEUROLOGIC DISORDERS: MIGRAINE HEADACHES

Primary headaches commonly affect reproductive aged women. Given concern over the risk of stroke with migraines and use of estrogen containing contraceptives, it is important to accurately classify headaches. Now in the beta version of its third edition, The International Classification of Headache Disorders from the International Headache Society is a reference for diagnostic criteria of different headache disorders.[126] Migraine headaches are divided into two major sub-types: migraine without aura and migraine with aura. Migraine without aura is described as a recurrent headache disorder with episodes lasting 4–72 hours. Migraine headaches have two of four defining characteristics (unilateral location, pulsating quality, moderate or severe pain intensity, and exacerbation with physical activity) and either nausea/vomiting or photophobia and phonophobia. Migraines with aura are classified by recurrent attacks of unilateral reversible visual, sensory, or other central nervous system symptoms that are followed by headache. The most common type of aura is visual, usually manifesting as a zigzag figure that may spread right or left with various degrees of scotoma. Aura is distinguished from premonitory symptoms that are not a true aura based on duration and timing. A true migraine aura starts and resolves before the onset of the headache and lasts less than an hour (usually 20–30 minutes). Premonitory symptoms can start 1–2 days before the headache and can include blurred vision and light sensitivity along with the more common symptoms of hyper- or hypo-activity, food cravings, yawning and neck stiffness. These symptoms may also continue during the headache, further differentiating these symptoms from true migraine aura. Premonitory symptoms do not need to be considered when determining the appropriateness of a contraceptive method in women with migraines.

Combined hormonal contraceptives

Migraine headache is an independent risk factor for ischemic stroke. A meta-analysis of 11 case–control and three cohort studies found an elevated risk of ischemic stroke in women <45 years old with a history of migraines (RR 2.76, 95% CI: 2.17–3.52).[127] Women who report migraines with aura appear to have a higher risk of stroke (RR 2.27, 95% CI: 1.61–3.19) compared to women who have migraines without aura (RR 1.83, 95% CI: 1.06–3.15).[127] COC users also demonstrate an increased risk of ischemic stroke. A meta-analysis of seven recent studies (five case–control and two cohort studies) found an odds ratio of 1.90 (95% CI: 1.24–2.91) of ischemic stroke in current COC users.[128]

Given that migraines and COCs both independently increase the risk of ischemic stroke, there is concern about the use of COCs in women with migraines. In fact, several case-control studies have reported a two to four-fold increased risk of ischemic stroke in women with migraines who use COCs compared to non-users with migraines.[129, 130, 131, 132, 133] Compared to COC non-users without migraines, women who use COCs and have migraines experience a six to fourteen-fold increase in stroke risk.[129, 131, 132] It is important to note that the quality of the studies range from intermediate to low. Some studies relied on self-report of migraine history instead of standard criteria, and there is a potential for recall bias of COC use.[134]

The studies are not adequately powered to determine the risk of stroke by migraine sub-type. However, it can be inferred that migraines with aura are associated with a higher risk of stroke than migraines without aura. Therefore, WHO recommends avoiding CHCs in women at any age who experience migraines with aura (WHO MEC category 4). The risk of stroke also increases with age. At age 20, the attributable risk of migraine and COC use to stroke is 8 per 100,000 women, whereas it is 80 per 100,000 women by age 40.[135] Accordingly, women <35 years old who have migraines without aura may initiate CHCs (WHO MEC category 2), whereas women ≥35 years should avoid initiation of CHCs (WHO MEC category 3). If a woman develops new headache or changes in headache quality, she should be evaluated. New migraine headaches while taking CHCs should prompt discontinuation of CHC use in both women <35 years old (WHO MEC category 3) and ≥35 years old (WHO MEC category 4).

An elevated risk of hemorrhagic stroke has not been demonstrated in COC users or women with migraines.[128, 134] Women with non-migraine headaches can use CHCs (WHO MEC category 1).

Progestin-only methods

Progestin-based contraceptive methods do not carry the same risk of ischemic stroke as do CHCs. In a 15-year Danish historical cohort study, there was no increase in stroke risk among women who used norethindrone (RR 1.35, 95% CI: 0.93–1.96), LNG-IUD (RR 0.73, 95% CI: 0.54–0.98), or implant (RR 0.88, 95% CI: 0.28–2.72) compared to women using no contraception.[15] Although the use of progestin-based methods in women with migraines is considered safe, there are limited data. One diary based pilot study evaluated the use of desogestrel in women who experience migraines with auras and found that the frequency of migraine episodes and duration of aura symptoms decreased over 6 months of use.[136] Progestin-based contraception is WHO MEC category 2 for initiating the method in women with migraines with aura. In women with migraines without aura or non-migraine headaches, progestin-based contraception is WHO MEC category 1. As in the case of CHCs, any new headaches or changes in headache characteristics warrant evaluation.

Intrauterine devices

No studies were identified that specifically examined the use of IUDs in women with migraines. However, Cu-IUD is considered safe to use in women with headaches (WHO MEC category 1), migraines without aura (WHO MEC category 1) and migraines with aura (WHO MEC category 1). Similarly, the LNG-IUD is appropriate for use in women with non-migraine headaches (WHO MEC category 1), migraines without aura (WHO MEC category 2), and migraines with aura (WHO MEC category 2). Again, any new headaches or changes in headache should prompt evaluation, and continuation of the LNG-IUD in women with migraines in aura is cautioned (WHO MEC category 3).

NEUROLOGIC DISORDERS: EPILEPSY

An increased risk of congenital malformations is seen in fetuses that are exposed to antiepileptic drugs (AEDs). For example, one study demonstrated a congenital malformation risk of 4.6% among women taking AEDs compared to a 2.8% risk among women with untreated epilepsy.[137] The most common malformations found among children with *in utero* AED exposure are neural tube defects, cardiac and genitourinary malformations, and cleft palate.[138] The malformation

pattern varies with the type of AED. For instance, valproate and carbamazepine exposure is associated with higher rates of neural tube defects, whereas maternal lamotrigine use results in an increased risk of neonatal oral clefts.[139] The sequela of phenytoin use has been described as the fetal hydantoin syndrome, a combination of dysmorphic features including hypoplasia of the distal phalanges, epicanthal folds, hypertelorism, and a broad flat nasal bridge.[138] These structural abnormalities arise during the organogenesis phase, which occurs between 3 and 8 weeks' gestation. Accordingly, contraception counseling to avoid an unplanned pregnancy is important in women taking AEDs. In addition, achieving optimal seizure control before pregnancy decreases the risk of seizure during pregnancy.[140] This further increases the importance of planned pregnancy in these women.

Combined hormonal contraceptives

Interactions between COCs and AEDs have been demonstrated as early as 1972.[141] Steroid hormones are metabolized by the hepatic cytochrome P450 enzyme system, especially by the 3A4 isoenzyme. Certain AEDs are enzyme inducers, increasing the metabolism of sex steroids and, subsequently, decreasing their efficacy. Furthermore, some AEDs increase the production of sex hormone binding globulins, decreasing the free contraception of sex hormones. The enzyme-inducing AEDs include: phenytoin, carbamazepine, phenobarbital, primidone, topiramate, oxcarbazepine, and felbamate.[142]

Several studies demonstrate pharmokinetic changes in sex steroid hormone levels with the addition of AEDs. One group of five women with severe epilepsy on various combinations of AEDs (including phenytoin, carbamazepine, primidone) taking 50 μg ethinyl estradiol/250 μg levonorgestrel contraceptive pills demonstrated lower serum concentrations of ethinyl estradiol and norgestrel, and higher levels of sex hormone binding globulin capacity.[143] A randomized, open-label study of women taking a low-dose COC (35 μg ethinyl estradiol/1 mg norethindrone) in cycle 1 followed by addition of carbamazepine in cycle 2 showed increases in mean clearance rates of both ethinyl estradiol (127%, p <0.05) and norethindrone (69%, p <0.05) as well as decreases in AUC values of ethinyl estradiol (42%, p <0.05) and norethindrone (58%, p <0.05).[144] Finally, a crossover study with 16 women taking a high-dose COC (50 μg ethinyl estradiol and 250 μg levonorgestrel) demonstrated lower peak plasma concentrations, AUC values, and half lives of ethinyl estradiol and levonorgestrel in women taking oxcarbazepine compared to placebo.[145]

Based on these studies, AEDs that induce the CYP3A4 isoenzyme result in decreases in sex steroid hormone levels and can subsequently reduce the effectiveness of COCs. Although there are no studies that specifically examine the effect of concurrent AED use on serum hormone levels in women using contraceptive rings and patches, the same precautions apply.[142] Therefore, CHCs are WHO MEC category 3 for use in women taking phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine.

Lamotrigine is not an enzyme inducer, however, it also has interactions with hormonal contraceptives. Lamotrigine is metabolized via conjugation with glucuronic acid, and estrogen derivatives appear to induce glucuronidation. Consequently, increased metabolism of lamotrigine occurs in the presence of estrogen-containing contraceptives. One study of 16 healthy women taking a COC with 30 μg ethinyl estradiol/levonorgestrel 150 μg and concurrent lamotrigine showed no change in ethinyl estradiol levels and a modest decrease in levonorgestrel levels with lamotrigine use (mean 12% decrease in peak plasma concentrations and 19% decrease in AUC).[146] However, a large decrease in serum concentrations of lamotrigine with concurrent COC use (mean decrease of 39% in peak plasma levels and 52% in AUC) was found.[146] Several other studies also report lower lamotrigine levels[147, 148, 149] and an increase in seizure activity[150, 151] in women taking COCs. Based on these studies, CHCs should be used with caution in women taking lamotrigine (WHO MEC category 3).

Progestin-only methods

As reviewed previously, enzyme-inducing AEDs decrease serum concentrations of both ethinyl estradiol and progestogens. Because progestin-only pills generally contain lower doses of progestin than doses found in combined oral contraceptive pills, there is a potentially high failure rate when taken in combination with enzyme-inducing AEDs.[142] As a result, progestin-only pills should be prescribed with caution (WHO MEC category 3).

Concurrent use of enzyme-inducing AEDs has not been shown to affect DMPA efficacy.[142] Furthermore, DMPA may also reduce seizure frequency in women with uncontrolled epilepsy.[152] DMPA is WHO MEC category 1 for women using enzyme-inducing AEDs.

On the other hand, contraceptive failure has been reported with the implant in women taking enzyme-inducing AEDs. Three studies described lower levels of levonorgestrel and increased risk of pregnancy in women taking enzyme-inducing AEDs with levonorgestrel implant.[153, 154, 155] Pregnancies have also been reported in women using the etonogestrel implant and enzyme-inducing AEDs, primarily carbamazepine.[156, 157] With these limited data, the implant is a WHO MEC category 2 for use in women taking enzyme-inducing AEDs.

In contrast to COCs, progestin-only contraceptive methods do not lower serum lamotrigine levels.[158] In women taking lamotrigine, progestin-only pills, DMPA, and implants are WHO MEC category 1.

Intrauterine devices

Although limited data exist regarding the use of IUD in women with epilepsy, it is considered an acceptable method of contraception in this group.[159] In an observational study of women taking enzyme-inducing AEDs and using the LNG-IUD, there were two unplanned pregnancies during 1075 months of exposure to pregnancy risk. One appeared to be a true contraceptive failure, while the second pregnancy was probably conceived after removal of the IUD. The authors calculated a failure rate of 1.1 per 100 woman-years if taking into account only the first unplanned pregnancy.[160] In women taking lamotrigine, mean serum lamotrigine levels did not differ between progestin-only contraceptive users (of which three were using the LNG-IUD) and non-hormonal contraception users.[158] Based on available evidence, both the LNG-IUD and Cu-IUD can be used without restriction in women with epilepsy, and both enzyme-inducing AED and lamotrigine users (WHO MEC category 1).

SUMMARY

In summary, most women with medical problems have effective contraceptive options that do not accelerate their disease process or affect medical therapy. These women do require a careful review of their medical history and a complete assessment of their current disease status. In consultation with the patient, the physician should develop an individualized reproductive health plan that addresses her specific disease process and prognosis, her risks from pregnancy, possible teratogenicity of her medical therapy, and the optimal time to plan for a future pregnancy. Effective contraception, although not necessarily risk-free, often represents a much safer alternative than an unplanned pregnancy.

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