Contraception for women with systemic lupus erythematosus

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OVERVIEW

Systemic lupus erythematosus (SLE) is an autoimmune disease of uncertain aetiology that can affect multiple organ systems. The disease is more prevalent in women, with a female:male ratio of about 10:1 in most studies. In some populations SLE incidence is highest in women of reproductive age, while in others the highest age-specific incidence rates in women are seen after age 40 years.[1] Globally, reported estimated prevalence rates in women range from 35/100 000 in a white subpopulation in the UK[2] to 694/100 000 in an African American subpopulation in the USA.[3] In general, a higher disease burden is found in non-white subpopulations worldwide.

Unfortunately, despite the complications that an unintended pregnancy can cause for a woman with SLE, many women with SLE are not counselled regarding contraceptive use or are counselled against contraceptive use based on concerns that contraceptives will adversely affect their disease. A recent study found that among a cohort of women with SLE and at risk of unintended pregnancy, including many on teratogenic medications, 59% reported no contraceptive counselling within the past year and 53% relied solely on barrier contraceptive methods.[4]

RECOMMENDATIONS

In the 2009 update of the World Health Organization *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC),[5] SLE was included for the first time as a condition. Recommendations were made by a working group of global family planning experts on the safety of contraceptive method use by women with SLE, based on a systematic review of the evidence (Table 1).[6] Each medical condition/contraceptive method combination is classified as one of four categories: Category 1 indicates no restrictions on the use of the method; Category 2 indicates the benefits generally outweigh the risks; Category 3 indicates the risks generally outweigh the benefits; and Category 4 indicates an unacceptable health risk if the method is used by women with the medical condition. Subsequent adaptations of WHOMEC for both the UK and the USA include the same recommendations for use of contraceptives by women with SLE.

Disease activity

Historically, one of the main concerns for women with SLE using hormonal contraceptives has been disease activity. The high female:male ratio during childbearing years has implicated estrogen in the development, and perhaps worsening, of SLE. In 2005, two randomised controlled trials (RCTs) were published that evaluated whether use of combined oral contraceptives (OCs) was associated with worsening SLE disease. A single-blind, non-placebo, RCT from Mexico[7] randomised 54 women with SLE to combined OCs (30 μg ethinylestradiol and 150 μg levonorgestrel), 54 to progestogen-only pills (30 μg levonorgestrel) and 54 to the TCu380A® intrauterine device (IUD). There was no difference in global disease activity at any of the follow-up points in any of the groups over 1 year, including a separate analysis of patients with active disease at baseline. The probability of any flare or severe flares was not different among the three groups. A multicentre, double blind, placebo-controlled trial randomised 183 women with SLE to either treatment with a 35 μg ethinylestradiol triphasic combined OC or an identical placebo.[8] The 12-month severe flare rate was not different between the two groups nor were any other measures of disease severity over the 12-month period. While neither of these trials included women with very severe disease, the results indicate that at least for women with quiescent or mild active

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Table 1 Summary table of recommendations for use of contraceptive methods by women with systemic lupus erythematosus (from the World Health Organization *Medical Eligibility Criteria for Contraceptive Use*[5])

Condition	COC	CIC	P/R	POP	DMPA		LNG/ETG Implants	Cu-IUD		LNG-IUS
Systemic lupus erythematosus					I	C		I	C	
(a) Positive (or unknown) antiphospholipid antibodies	4	4	4	3	3	3	3	1	1	3
(b) Severe thrombocytopenia	2	2	2	2	3	2	2	3	2	2
(c) Immunosuppressive treatment	2	2	2	2	2	2	2	2	1	2
(d) None of the above	2	2	2	2	2	2	2	1	1	2

C, continuation; CIC, combined injectable contraceptives; COC, combined oral contraceptives; Cu-IUD, copper-releasing intrauterine device; DMPA, depot medroxyprogesterone acetate; ETG, etonorgestrel; I, initiation; LNG, levonorgestrel; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; P/R, combined hormonal patch or ring.
World Health Organization *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC) Categories 1–4 are as defined in the main text.

disease, use of hormonal contraceptives, either combined estrogen and progestogen or progestogen-only, does not seem to worsen disease activity.

Thromboembolism

Another significant area of concern for use of hormonal contraceptives by women with SLE is the risk of thromboembolic events. Thromboembolism, both arterial and venous, is a major cause of death in people with SLE.[9] This risk for thromboembolism is further increased by the presence of antiphospholipid antibodies.[10] The use of combined hormonal contraception is known to increase venous thromboembolism (VTE) risk in healthy reproductive age women.[11] Very few studies have evaluated hormonal contraceptive use and risk of VTE in women with SLE. A case-control study of 157 participants (including 131 women) with positive antiphospolipid antibodies (most of whom also had SLE) found a trend toward increased risk of thrombosis, particularly arterial, in those with reported use of OCs.[12] None of the values were statistically significant but the study was not powered to look at this exposure. In a prospective cohort study of 65 women with SLE and positive antiphospholipid antibodies, all women with a history of OC use (type unspecified, $n=3$) developed a thrombotic event whereas only 23 of the 62 women without a history of OC use developed a thrombotic event.[13] While there are very few data specifically evaluating the risk of VTE women with SLE using progestogen-only contraceptives, data from healthy women as well as from women with known thrombophilias indicate that the risk of VTE with progestogen-only contraceptives, if any, is significantly lower than that with use of estrogen-containing methods.[14] Therefore, progestogen-only contraceptives are considered safe for women with SLE, with the exception of those with positive antiphospholipid antibodies who are at the greatest risk of VTE.

Benefits of contraception in women with SLE

An important factor to consider when discussing the safety of contraceptives for women with SLE is the alternative of pregnancy. Several studies have found a two- to three-fold increase in disease activity during pregnancy in women with SLE.[15 16] Pregnancy complications are more frequent in women with moderate to severe disease during pregnancy.[17] Therefore, it is of the utmost importance that wanted pregnancies in women with SLE are planned and ideally occur at a time of disease quiescence. Women with SLE who wish to avoid pregnancy should be adequately informed about the risks and benefits of available contraceptive options in the context of the risks associated with pregnancy.

Many contraceptive options also can provide non-contraceptive benefits to women with SLE. A prospective cohort study evaluated musculoskeletal complication among 407 women with SLE from Johns Hopkins.[18] Oral contraceptive use was associated with decreased risk of musculoskeletal damage in this study, though no information on duration or timing of OC use with respect to the diagnosis of SLE was reported. An additional retrospective cohort study of 702 women with SLE evaluated the association of ever use of OCs (type not specified) with fracture risk.[19] The authors reported that women who had never used OCs had a greater likelihood of fracture than those with a history of OC use. Women with SLE may also be at increased risk for heavy menstrual bleeding or haemorrhagic ovarian cysts due to treatment with anticoagulants or development of thrombocytopenia. In these women, treatment with hormonal contraceptives, including the levonorgestrel-releasing IUS, may provide protection from these side effects of treatment or complications of the disease, due to suppression of ovulation and/or decreased menstrual bleeding.[20 21]

CONCLUSIONS

The primary risks from use of hormonal contraceptives in women with SLE involve thrombogenic risks, particularly in those women with antiphospholipid antibodies. The best available evidence does not indicate a risk of worsening disease activity in women with mild to moderate SLE who use hormonal

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contraceptives, either combined or progestogen-only. As outlined in WHOMEC and the adaptations for the US and UK, with the exception of women at increased risk for thrombosis due to antiphospholipid antibodies, the benefits of contraception outweigh the risks for most women with SLE.

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