Best Practice & Research Clinical Obstetrics and Gynaecology 60 (2019) 111–123

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Contraception in autoimmune diseases

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Keywords:
Autoimmune diseases
Steroid hormones
Hormonal contraception
Intrauterine devices
Medical eligibility criteria

A B S T R A C T

Autoimmune diseases (AIDs) affect women and men with a 2:1 ratio, which suggests that hormonal contraceptives play a role in their clinical course.

Combined oral contraceptives have complex, sometimes contradictory, effects on AIDs; they can worsen the situation in women with systemic lupus erythematosus and with anti-phospholipid syndrome, conditions in which they are contraindicated. Early studies indicated a positive effect on rheumatoid arthritis (RA), whereas more recent trials failed to do so, possibly because of the lowering of oestrogen content. Evidence of effects on multiple sclerosis (MS) is conflicting: risk may vary depending on the progestin used. Minor adverse effects may exist on inflammatory bowel diseases, and no significant effect was found on autoimmune thyroid diseases. Women can become sensitised to sex hormones.

Progestin-only contraceptives may be used, although copper-releasing intra-uterine devices represent the best option.

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https://doi.org/10.1016/j.bpobgyn.2019.05.003

Finally, several organisations have issued guidelines for contraceptive use in women with AIDs.

Introduction

Contraceptive methods are usually classified according to their duration of action, reversibility and mechanism of action; they can be classified as '*hormonal*' and '*non-hormonal*'. Autoimmune diseases (AIDs) often respond to hormonal stimuli (specifically, sex hormone steroids), and their course may be modified by pregnancy or the use of hormonal contraceptive methods such as oral pills, patches, injections, implants or intra-uterine progestin-releasing systems. Hence, in evaluating both the choice of method of family planning for young women with an AID (who are often fertile and require protection from unwanted pregnancies) and the possible side effects, one must distinguish between the two categories.

Women with AIDs often do not use contraception. An early, Finnish survey found that contraceptive use was less in patients with systemic lupus erythematosus (SLE) than that in healthy subjects of the same age (59% vs 77%, $P < 0.001$). When using contraception, preference was often given to barrier and natural methods ($P < 0.001$) [1]. A 2011 study of 206 women with SLE conducted in the USA found that 42% were at risk of unwanted pregnancy and almost two-thirds had not been given any advice about contraception during the previous year. Only 22% were 'inconsistently' using a contraceptive and 53% relied only on barrier methods. The most appropriate method, an intra-uterine device (IUD), was utilised by a mere 13%. Even more alarming was the fact that patients receiving potentially teratogenic drugs were unlikely to have received contraceptive counselling [2]. Data on SLE and rheumatoid arthritis (RA) are also available from Sri Lanka: unplanned pregnancies were significantly more frequent ($P < 0.01$) in SLE than in RA, and contraceptive usage was lower in patients with SLE (25.6%) and RA (33%) than in those with no chronic illnesses (56.4%) [3]. A very recent investigation from Brazil involved 85 women with SLE with a mean age of 33 years [4] and found that before diagnosis, most women used some contraceptive method [54% a combined oral contraceptive (COC) and 21% an unspecified 'hormone injection']. Following diagnosis, 53% of patients did not use any contraceptive method. The authors concluded that although two-thirds of these patients regularly consulted a gynaecologist, the majority (56%) were unaware of which contraceptive method would be optimal.

Another major issue is the large number and varying frequency of conditions that go under the comprehensive label of 'autoimmune diseases'. A recent, very informative review by Williams on *Hormonal contraception and the development of autoimmunity* [5] pointed out the complete lack of '*relevant literature for a number of the less frequent autoimmune diseases*'. However, in the case of the more frequent conditions [RA, SLE, Crohn's disease (CD), ulcerative colitis (UC), multiple sclerosis (MS), autoimmune thyroid disease (ATD) and immune skin diseases], controlled trials have been carried out and the effect of contraceptive methods (mostly hormonal) has been properly evaluated. In this context, it is important to stress that, overall, women are affected by an AID more often than men, with a 2:1 ratio. A few years ago, Hayter and Cook [6] listed 81 different AIDs and estimated their prevalence at 4.5% (2.7% for males and 6.4% for females).

The present review focuses on the effect of sex hormones on women with an AID, on their response to hormonal methods and on non-hormonal options open to them.

Combined oral contraceptives

Given the multiple and, at times, contrasting effect that steroid hormones have on individual AIDs, it is not surprising that the action of COC is complex and, at times, contradictory, mostly depending on the type of immune response involved in a single AID immunopathologic process. Additionally, in the 60 years of COC use, their composition has varied in both qualitative and quantitative terms. Until

recently, most COCs contained the same synthetic oestrogen ethinyl-oestradiol (EE). However, the oestrogen dose has been reduced from 150 μg of mestranol (corresponding to approximately 120 μg EE) to 20 μg or 15 μg [7]. Presently, more 'natural' oestrogens (oestradiol-17β, oestradiol valerate and oestetrol) have been introduced [8–10], but there is a complete lack of information regarding their effect on AIDs.

The situation is even more complex regarding the progestin component. A variety of compounds with different chemical structures, pharmacodynamic properties, biological activity and side effects have been used in COCs. They can be grouped into four distinct families [11,12] and vary in their daily dosage from 3 mg to 60 μg. Additionally, different regimens of administration (mono-, bi-, tri- and even tetra-phasic) and duration of administration (21–24 days) have been used.

Multisystemic disorders

Systemic lupus erythematosus

Studies published over the last 40 years have accumulated evidence that COC can exacerbate SLE. Jungers et al. [13,14] found exacerbations of the disease in 44% of their cohort, including major renal histological lesions. A negative effect was also found by Julkunen [15] in 4 out of 85 subjects using a COC with 30 μg EE, again with major renal involvement. In 1997, Petri and Robinson [16] cautioned and argued that, although discontinuation of COC was the usual practice when SLE is diagnosed, COC offered potential beneficial effects including effective contraception, control of cyclic SLE disease activity and prevention of osteoporosis. In fact, in 2005, a cooperative, multicentre study by a consortium led by Petri [17] evaluated the use of COC over 12 months in 183 women with inactive (76%) or stable active (24%) SLE. They were assigned to either a triphasic pill [EE at a dose of 35 μg and norethisterone (NET) at increasing doses of 0.5–1 mg for 12 cycles or placebo]. Severe lupus flare occurred in 7.7% of COC users vs 7.6% in the placebo group, indicating no significant difference. In another multicentre study, Sánchez-Guerrero et al. [18] randomly assigned 162 women with SLE to COC, progestin-only contraceptive (POC) or a copper-releasing IUD (Cu-IUD). They found that disease activity remained mild and stable in all groups throughout the trial, leading to the conclusion that no differences could be found in any of the three groups.

Anti-phospholipid syndrome

Anti-phospholipid syndrome (APS) is characterised by antibodies to negatively charged phospholipids in the placenta and small blood vessels and shows an overlap with SLE by 40% [19]. Julkunen [15] reported two cases of deep venous thrombosis in patients with positive anti-phospholipid antibodies (aPL) who were taking COC. The presence or absence of aPL predisposes to thromboembolic complications [20]. Cervera et al. [21] reported the incidence of thrombosis as high as 30% in patients with APS. A large multicentre population-based case–control study named RATIO (Risk of Arterial Thrombosis In relation to Oral contraceptives) found the presence of 'lupus anticoagulant' in 17% of patients with ischaemic stroke, in 3% of those with myocardial infarction and 0.7% among controls [22]. Hence, in APS, oestrogen-based contraceptives are best avoided. Progestin-only contraceptives do not have such a pro-thrombotic effect and can be used instead. However, it may be best to avoid hormone-based contraceptives altogether and use a Cu-IUD or barrier methods.

Rheumatoid arthritis

Forty years ago, an investigation by Wingrave and Kay concluded that the use of high-dose COC was associated with a lower incidence of RA [23]. This finding was confirmed in 1982 by Vandenbroucke et al. [24], who, after adjusting for possible confounding variables, found a rate ratio of 0.42 (95% confidence interval (CI) 0.27–0.65) for ever-use, 0.40 (0.22–0.72) for ex-users and 0.45 (0.28–0.75) for current users. The same group subsequently published additional evidence of a positive effect [25]. More recently, Doran et al. [26] carried out a population-based case–control study and observed an inverse association between ever-use of COC and the risk of RA (OR = 0.56; 95% CI 0.34–0.92). Interestingly, they stated that '*Earlier calendar-year of first exposure to OC was associated with lower OR for RA*'. This may indicate a greater effect of COC containing higher oestrogen doses.

In contrast to these findings, Williams [5] mentions 25 investigations failing to show significant differences. Among the most significant, two case–control studies were from Sweden, one by Pikwer et al. [27] and the other by Berglin et al. [28]; Pikwer et al. [27] found that prolonged breastfeeding reduced the risk of RA, whereas there was no change in the risk of RA with COC use. However, Berglin et al. [28] observed an increased risk of RA with increasing breastfeeding duration and a reduced risk in COC users. A subsequent Chinese investigation [29] concurred with Pikwer et al. [27] results. Breastfeeding was associated with half the risk of RA, and the risk decreased with increasing duration of breastfeeding (for at least 36 months); [OR = 0.54 (95% CI: 0.29–1.01) p for trend = 0.04], whereas COC use had no effect on RA. Finally, one report by Pedersen et al. [30] of a Danish national case–control study identified a series of RA subtype-specific risk factors; among them, an increased risk for ever-use of COC (OR = 1.65; 95% CI: 1.06–2.57) was found among subjects with auto-antibodies to cyclic citrullinated peptides (CCP). They concluded that the existence of major differences in risk factor profiles suggests a different aetiology for RA in anti-CCP-positive and anti-CCP-negative subjects.

Four meta-analyses have been carried out: the first, published 30 years ago, after examining summary statistics for case–control studies, concluded the existence of a small, not statistically significant, protective effect [31]. The following year, a second meta-analysis [32] evaluated 9 studies meeting their criteria and found an overall OR of 0.73 (95% CI: 0.61–0.85) for adjusted results. A separate analysis of studies with hospital-based cases by the same authors found an OR considerably lower than that of population-based cases [0.49 (95% CI: 0.39–0.63) and 0.95 (95% CI: 0.78–1.16)], concluding that COC use may not have a 'protective effect' on RA but may block disease progression. The third meta-analysis specifically tried to evaluate discrepancies among the two previous meta-analyses and observed a strong indication of heterogeneity when combining all studies ($x2 = 29.34$, p=0.00060), mostly due to selection of controls. They found no conclusive evidence of a protective effect [33]. The fourth meta-analysis, dated from 2014 [34], evaluated 12 case–control and five cohort studies and found no statistically significant association between COC use and the risk of RA (relative risk (RR) = 0.88; 95% CI = 0.75–1.03). When considering geographic areas, a borderline significantly decreased risk was observed for users in European studies (RR = 0.79; 95% CI = 0.62–1.01), not in trials conducted in North America (RR = 0.99; 95% CI = 0.81–1.21).

In conclusion, it seems that early studies showed a positive effect of COC, whereas more recent trials failed to do so. Whether, and to what extent, this may be due to lowering of the EE content in COC is at present unclear.

Predominantly organ-specific disorders

Autoimmune thyroid disease

The effect on thyroid function was one of the first pharmacodynamic actions ever studied in hormonal contraception. Over 50 years ago, Winikoff and Taylor [35] reported that COC use was 'invariably found to influence' seven of the thyroid tests in use at that time. They further found that 'the changes were proportional to the quantity of oestrogen contained in the COC studied'. Another early investigation conducted by Mishell et al. [36] found changes that 'approached hyperthyroidism levels'. These were attributed to the oestrogenic component. L'Hermite and Hubinont [37] subsequently reported that COCs affected the thyroxin-binding globulin (TBG) capacity of serum but that free thyroid hormones were altered only slightly, with peripheral thyroid function remaining unchanged.

More recently, Raps et al. [38] found that users of the COC that they considered 'most thrombogenic', namely, those containing desogestrel (DSG), cyproterone acetate or drospirenone (DRS), had higher TBG levels than users of COC believed to be less thrombogenic (*i.e.* the levonorgestrel (LNG)-releasing IUD). Raps et al. [38] also confirmed that thyroid-stimulating hormone levels were not significantly modified and free thyroxin levels did not change, concluding that modern COC do not influence the size and function of thyroid gland in healthy women.

However, in ATD disease, early investigations documented that both pregnancy and the use of COC led to cell-mediated immunosuppression, with a temporary remission of the condition and a gradual reduction of serum anti-thyroid antibody titres as the pregnancy progressed. This was followed by an increase during the postpartum and a recurrence of the disease [39–41].

In 1978, Frank and Kay [42] published the results of a cohort study of some 23,000 current or former COC users and a similar number of controls. They observed that all clinical groups of thyroid disease (benign thyroid swelling, thyrotoxicosis and myxoedema) were reported less frequently in users than in controls. An overall highly significant RR of 0.68 (P < 001; 95% CI 0.52 to 0.85) was found. Interestingly, thyroid disease rates in ex-users did not differ from controls and reporting rates did not correlate with oestrogen or progestogen dosage or with the duration of COC use. Twenty-five years later, Strieder et al. [43] carried out another large prospective cohort study of first- or second-degree female relatives of patients with documented ATD. They found that oestrogen use was associated with a lower rate of hyperthyroidism [RR 0.169; (95% CI) 0.06–0.52]; in addition, oestrogen use was negatively correlated with the presence of thyroid peroxidase auto-antibodies. According to Williams [5], there is no published evidence of any significant effect of COC on the subsequent development of hypothyroidism.

Multiple sclerosis

Early studies of the effect of COCs on MS have yielded conflicting results: no effect [44], a non-statistically significant slightly increased risk [45,46] and a protective effect [47]. More recently, Kotzamani et al. [48] evaluated a number of variables, comparing 657 patients with MS to 593 randomly matched controls, and found that patients with MS used COC more often than controls. Hellwig et al. [49] have compared 400 subjects with MS to 3904 matched controls and found a slightly increased risk of MS among users. Risk varied with the progestin in the COC: The odds ratio (OR) was 1.75 for LNG [95% CI: 1.29–2.37; $p < 0.001$] and 1.57 [95% CI: 1.16–2.12; $p = 0.003$] for NET. No increased risk was found when the COC contained the 4th-generation progestin DRS ($p = 0.95$).

In conclusion, no clear trend emerges, although the hypothesis has been put forward that COCs may be in part responsible for the increasing incidence of MS in women but not in men [50]. In a recent review meant to guide patients with MS in choosing a contraceptive, Houtchens et al. [51] concluded that most contraceptive methods appear to be safe for women with MS. The only exception is for patients with prolonged immobility because of the concern regarding possible venous thromboembolism.

Inflammatory bowel diseases

In 1995, Godet et al. [52] reported from a meta-analysis a RR increase of 1.44 (1.12–1.86) for developing CD and 1.29 (0.94–1.77) for UC in COC users. A second meta-analysis by Cornish et al. [53] found for current COC users a pooled RR of 1.51 for CD (95% CI: 1.17–1.96, $P = 0.002$) and 1.53 for UC (95% CI: 1.21–1.94, $P = 0.001$). For CD, the RR increased with COC length of exposure, whereas once discontinued COC use, the RR was no longer significant for either CD or UC.

Crohn's disease. Until 2017, 17 individual trials evaluated a possible relationship between use of COC and the development of an inflammatory bowel disease, all concluding that they had a negative effect on the condition [5]. Katschinski et al. [54] reported in a case–control study an RR of 2.5 (1.0–6.6), after 1–3 years of use and 4.3 (1.3–14.4) for more than three years of use. Interestingly, they found that COC increased the risk for CD only in nonsmokers. A subsequent population-based investigation [55] confirmed an increased risk in users ($p = 0.048$; OD 2, 8, 95% CI) but the increased risk disappeared in a multivariate analysis. More recently, Khalili et al. [56] reported from a prospective cohort study that the multivariate-adjusted hazard ratios (HR) for CD were 2.82 (95% CI: 1.65–4.82) among current users and 1.39 (95% CI 1.05–1.85) among past users compared to never users of COC. Finally, Ng et al. [57] found that in discordant twins, use of COC was associated with an increased risk (OR 4.0; 95% CI: 1.1–14.2).

Ulcerative colitis. Until 2017, 14 primary studies have been published that evaluated the effect of COC on the development of UC [5]. In an early study, Boyko et al. [58] evaluated the effects of COCs on 211 patients with UC against age-matched controls in a population-based case–control study. Use within 6 months before onset of the disease increased the UC risk (RR = 2.0, 95% CI 1.2–3.3). Adjustment for race, smoking, income or pregnancy history did not substantially alter these results. Risk tended to be

greater among users of high-dose oestrogen preparations. Subsequently, Parrello et al. [59] in a large, multicentre investigation reported that COC users had 3.11 times significantly greater risk of UC than non-users.

Other autoimmune conditions

Skin diseases

Women can become sensitised to their own sex hormones or to their synthetic analogues [60]. The existence of hypersensitivity was first documented in the form of a '*cyclic urticaria*' associated with menses in 1921, during the time when oestrogens and progesterone had not yet been isolated [61]. Premenstrual syndrome (PMS) has also been associated with a concomitant skin disease including pruritus vulvae, hyper-pigmentation, papular pruritic eruption and acne vulgaris [62]. Immediate and delayed hypersensitivity reactions to sex hormones were observed, with desensitisation producing a decrease in PMS symptoms and improvement in the skin disease. The hypersensitivity to progesterone seems paradoxical because progesterone and C_{21} synthetic progestins exert a suppressive action on the immune system. The appearance of the condition has been reported for NET, medroxyprogesterone acetate (MPA), norgestrel [63], depot-medroxyprogesterone acetate (DMPA) [64,65], etonogestrel (ETG) released daily from a vaginal ring at the rate of 120 μg [66] and progesterone as an intravaginal gel [67].

Progestins are best avoided in these patients in whom contraception with an IUD or a barrier method is the preferred choice.

Women can also become sensitised to their own oestrogens, as shown by positive intradermal skin tests against oestrogens. This phenomenon should be suspected whenever there is a worsening of the skin problem before menstruation. Shelley et al. [68] have reported that tamoxifen is the specific therapy. Other treatments such as the use of progestin-only pills [69], leuprolide [70] and even oophorectomy [71] have also been recommended. As expected, COC are contraindicated in these subjects and, here again, use of an IUD or a barrier method should be recommended.

Progestin-only contraception

Progestin-only contraceptives (POCs) can be administered by different routes. The oral route is used for the so-called 'minipill'. Two progestins are currently marketed as minipills: NET (*Micronor, Nor-QD, Noriday*) and DSG (originally *Cerazette*). The subcutaneous route is used for long-term administration of LNG (*Norplant, Jadelle*) or Etonorgestrel (ETG) (*Implanon, Nexplanon*). Two additional progestins can be administered intramuscularly: norethisterone oenanthate (NET-EN) and DMPA. It is worth noticing that MPA has a higher relative binding affinity for the glucocorticoid receptor (GCR) and much greater glucocorticoid potency than NET or progesterone. The GCR effect should be considered when discussing POC in patients with an AID; unfortunately, GCR-related effects have not been studied in the affected population.

Progesterone enhances Th2 and Treg activity and decreases Th1 and Th17 activity, which may explain the observed remission of Th1-type-AID, such as RA and MS, during pregnancy. Hence, progestins have potential in the treatment of these diseases [72]. Since the early work of Jungers et al. [13,14] involving 11 women (5 on NET minipill and 5 on 'discontinuous progestogen at normal dosage') followed up to 30 months, no negative consequences were observed when POC was administered to women with SLE. Unfortunately, no controlled trials of the effects of individual POC have been carried out in patients with RA or MS. There is, however, one large cohort study that attempted to comparatively evaluate the risk of developing an AID following initiation of use of the LNG-releasing contraceptive implant (LNG-I) *vs* a Cu-IUD or sterilisation [73]. For practical reasons, rather than evaluating individual diseases, the study combined together conditions according to the Ninth Revision (ICD-9) of the International Classification of Diseases [74]. The study observed a significantly increased risk of developing 2 ICD-9 categories of diseases: 'rheumatism excluding the back' and 'arthropathies and related disorders', following medication with the LNG-I, compared to the insertion of the Cu-IUD or sterilisation. The 2 ICD-9 diagnostic categories include RA, diffuse diseases of connective tissue, arthropathies and poly-arthropathies. Among dermatological conditions connected with immune

disturbances, there was a significantly increased risk for eczema, contact dermatitis, pruritus, acne and urticaria. Finally, disorders of the thyroid gland occurred with the same frequency in women initiating the LNG-I compared to sterilised subjects, or those using a Cu-IUD. This remained true even after adjustments.

There may be a possible association between the use of POC and the development of vulval lichen sclerosus (VLS). Higgins and Cruickshank [75] have performed a case–control study of aetiological factors associated with VLS. They found that initiating POC specifically decreases the risk of subsequently acquiring VLS (OR = 0.19, $p = 0.045$); the negative association became less significant when corrected for age. Interestingly, whereas COC use was negatively associated with VLS, the association became non-significant when corrected for current age.

Intra-uterine devices and systems

Two types of intrauterine contraceptives are in widespread use today: the Cu-IUD-releasing copper ions [76] and the LNG-IUD-releasing LNG [77]. Either type probably represents the best option for women with an AID, as the copper-releasing device is devoid of any hormonal activity and the action of the progestin in the LNG-IUD is exerted mostly within the reproductive tract and the circulating levels of the progestin do not inhibit ovulation [78].

Unfortunately, a search of the literature on the use of an IUD in women with an AID provided only scant information. A randomised, prospective study by Sanchez-Guerrero et al. [18] found that insertion of the Cu-IUD in women with SLE did not change disease activity or the incidence of lupus flares. In addition, the Cu-IUD did not seem to increase the risk of severe infections [73]. The point about infections is debatable, as more patients with a Cu-IUD developed severe infections than users of COC or POC; however, two out of five of these infections did not involve the reproductive tract. No direct data seem to exist on the use of the LNG-IUD in women with an AID. There is, however, one report on a rare condition, Evans syndrome (combined autoimmune haemolytic anaemia and thrombocytopaenia or neutropaenia), that may have been related to exposure to a polyethylene-based IUD [79]. There is also a report of a case of 'progestogen hypersensitivity' manifested within 24 h of the insertion of an LNG-IUD [80]. Attempts at treating the symptoms were initially partially successful, but 45 days after insertion, the device had to be removed, with quick resolution of the clinical presentation.

Over 30 years ago, there were case reports of Cu-IUD failure in women using immunosuppressive agents, following renal transplant. IUD failure may have been due to immunosuppressive agents altering the immune response generated by the IUD, hence reducing its efficacy [81]. Julkunen et al. [1] reported that women with SLE tended to use barrier and natural methods (only 12% used the Cu-IUD), leading to the conclusion that both physicians and patients feared the development of infections. However, more recent investigations do not link IUD use to an increased risk of infectious morbidity in immune-compromised women [82].

In conclusion, any judgement on the risk and benefits of using an IUD in women with an AID is based more on assumptions than on facts. However, large cohort studies of the risk of developing an AID with a LNG-releasing contraceptive implant found that use of a Cu-IUD had the same effect as sterilisation, that is, it had no negative consequences [83].

Medical eligibility criteria for contraceptive use in women with AID

Presently, a number of guidelines exist to assist health personnel in advising women on the optimal method of family planning for them. Guidance was first provided by the World Health Organization (WHO), and this was followed by a number of individual countries, among them being the USA and the UK.

In these guidelines, methods are divided into 4 categories:

1. No restriction for use;
2. Advantages generally outweigh theoretical or proven risks;
3. Theoretical or proven risks usually outweigh the advantages;
4. A condition that represents an unacceptable health risk for using a method.

World health organizsation

To improve family planning quality of care, the WHO started publishing 'guidance manuals' that summarise the safety of various contraceptives when used by women with specific health conditions. The most recent edition of these '*Medical eligibility criteria for contraceptive use*' (MEC) was published in 2015 and is the latest in a series of periodic updates [84]. It aims at providing information whether a given contraceptive has no effect, worsens the medical condition or induces additional health risks. The criteria also evaluate whether the condition or its treatment may make a contraceptive method less effective. In this context, it must be always borne in mind that for any situation, medical risks should be weighed against the benefits of preventing pregnancy. In addition, the method utilised may modify the severity of the medical condition in itself (as is often the case with AID).

Detailed as it may be, the MEC provides only limited information of AIDs. In fact, the MEC mentions only SLE and under the category 'Rheumatic Diseases'; in this group, however, there is no reference to RA (Table 1). The conclusion to be drawn for women suffering from SLE is that if aPL are present, COC represent an unacceptable health risk, and therefore, they are absolutely contraindicated (*category 4*). aPL confer a significantly increased risk of vascular thrombosis [20–22,85,86], above the increased likelihood found in all COC users (see, e.g. [87]).

Progestin-only contraception is also not recommended if aPL are present (*category 3*), for the same reason.

In conclusion, according to the WHO, for women with SLE and aPL, the best method of contraception is the insertion of a Cu-IUD but not an LNG-IUD. However, even a Cu-IUD may be contraindicated if severe thrombocytopaenia is present, as the device increases the quantity of menstrual blood loss. Given that these women need protection against unwanted pregnancy, the WHO recommends the use of the LNG-IUD because it reduces menstrual bleeding [88].

Table 1
WHO, MEC, 2015, modified.

	COC	P	CVR	CIC	POP	Cu-IUD	LNG-IUD
Rheumatic diseases							
Systemic lupus erythematosus (SLE)							
a) Positive (or unknown) antiphospholipid antibodies	4	4	4	4	3	1	3
b) Severe thrombocytopenia	2	2	2	2	2	3	2
c) Immunosuppressive treatment	2	2	2	2	2	2	2
d) None of the above	X'2	2	2	2	2	1	2

COC = combined oral contraceptive. P = combined contraceptive patch. CVR = combined contraceptive vaginal ring. CIC = combined injectable contraceptive. POP = progestogen-only pill. Cu-IUD = copper-releasing IUD. LVG-IUD = levonorgestrel-releasing IUD (20 mcg/24 h).

Table 2
US MEC, 2016, modified.

	CHCs	DMPA	Cu-IUD	LNG:IUD	POP	IMPLANTS
Multiple sclerosis						
a. With prolonged immobility	3	2	1	1	1	1
b. Without prolonged immobility	1	2	1	1	1	1
Rheumatic diseases						
Systemic lupus erythematosus						
a. Positive (or unknown) anti-phospholipid antibodies	4	3	1	3	3	3
b. Severe thrombocytopaenia	2	3	3	3	2	2
c. Immunosuppressive therapy	2	2	2	2	2	2
d. None of the above	2	2	1	2	2	2
Rheumatoid arthritis						
a. Receiving immunosuppressive therapy	2	2/3	2	2	2	1
b. Not receiving immunosuppressive therapy	2	2	1	1	1	1

CHC= Combined hormonal contraceptives including pill, patch and ring. DMPA = depot medroxyprogesterone acetate. Cu-IUD = copper-releasing intrauterine device. LNG-IUD = levonorgestrel-releasing intrauterine device. POP = progestin-only pill.

Table 3
UK MEC, 2017, modified.

	CHCs	DMPA	Cu-IUD	LNG:IUD	POP	IMPLANT
Rheumatic diseases						
Systemic lupus erythematosus						
a. No anti-phospholipid antibodies	2	2	1	3	2	2
b. Positive anti-phospholipid antibodies	4	2	3	3	2	2
Rheumatoid arthritis	2	2	1	2	2	2

CHC= Combined hormonal contraceptives including pill, patch and ring. DMPA = depot medroxyprogesterone acetate. Cu-IUD = copper-releasing intrauterine device. LNG-IUD = levonorgestrel-releasing intrauterine device. POP = progestin-only pill.

Centers for Disease Control and prevention U.S.A.

The United States Centers for Disease Control and Prevention (CDC) have also published useful information for contraception by women with AIDs. The 2016 edition [89] presents four main tables, which are summarised in Table 2. For women with MS, for prolonged immobility, DMPA has been assigned to *category 2* and COC to *category 3*; otherwise, all methods are safe.

In their second table, they detail the criteria for use of an IUD in women with SLE. Similar to the advice of the WHO, the CDC distinguishes between women testing positive or negative for aPL. The former is at increased risk for cardiovascular diseases; therefore, whereas the Cu-IUD is listed as *category 1*, the LNG-IUD was assigned to *category 3*, which is probably excessive. If no aPL or cardiovascular risk factors are evident, then the majority of women with SLE can utilise most contraceptive methods, including COC, unless they are on immunosuppressive therapy.

In patients with RA, the insertion of either type of IUD is permitted (*category 2*), and continuation does not pose a problem. Although autoimmune thyroiditis is not singled out, no increased risk is assigned to 'hypothyroidism'.

Criteria for use of POC, including implants, DMPA and minipills, are provided in the third table. In subjects with SLE testing positive for aPL, the use of any POC is discouraged (*category 3*). Utilisation is permitted (except DMPA) if the disease is associated with severe thrombocytopaenia, or the patient is treated with immunosuppressive therapy (*category 2*). In women suffering from RA and receiving immunosuppressive therapy, subcutaneous implants and minipills are encouraged (*category 1*), whereas DMPA use is contraindicated if the patient is under long-term corticosteroid therapy and has a history, or risk factors, for non-traumatic fractures (*category 3*). In women not receiving immunosuppressive therapy, all POCs can be used. There is no contraindication to the use of POC in subjects with hypothyroidism.

The last table is dedicated to combined hormonal contraceptives (CHC), including COC, patches and rings. There is no mention of monthly combined injectables (such as Cycloprovera or Cyclofem). For women with SLE and aPL, the contraindication to all varieties of CHC is absolute (*category 4*). In the absence of aPL, all CHCs are permitted (*category 2*) even if the patient receives immunosuppressive treatment or has severe thrombocytopaenia (*category 2*).

In women with RA, CHC are permitted (*category 2*). Finally, no limitations exist in the event of hypothyroidism.

Faculty of Sexual and Reproductive Healthcare of the UK

The last edition of the United Kingdom Medical Eligibility Criteria (UKMEC) for contraceptive use was published in 2017 [90]. The UK decided to issue its separate MEC to adapt the WHO-MEC for use in the UK, in which the risk–benefit ratio of the various methods may be different from that in the global population.

The UKMEC lists only two absolute contraindications (*category 4*), (Table 3): both for use of CHC: SLE positive for aPL; and the presence of aPL, irrespective of any other condition. Everything else is permitted (either *category 1 or category 2*).

Conclusions

After a thorough search, Williams [5] reached the conclusion that there is no relevant information of the effects of contraceptive methods for a number of the less frequent AIDs. At the same time, for some of these diseases, there is some indication of a link to hormonal contraception.

Sufficient information for reaching a conclusion exists only for COC use in a few AIDs, mostly SLE, MS, RA, inflammatory bowel, thyroid and skin diseases.

Unfortunately, information is almost completely absent when it comes to the use of IUDs, the method of choice for the majority of female patients with AID.

Conflict of interest statement

The authors declare to have no conflict of interest with the content of this review.

Practice points

- Hormonal contraceptives may positively or negatively influence the course of an autoimmune disease (AID) depending on the type of immune mechanism involved in its pathogenesis.
- World Health Organization, Centers for Disease Control and Prevention (USA) and Faculty of Sexual and Reproductive Healthcare of UK among others have produced contraceptive guidelines for women with health conditions including a few AIDs.
- Combined hormonal contraceptives are usually contraindicated in women with AIDs.
- The best methods for women with AIDs are IUDs, including both those releasing copper and those releasing levonorgestrel.

Research agenda

- Theoretically, intrauterine contraception should be considered ideal for women with an autoimmune disease (AID). Yet, there is virtually no information of the effects of intra-uterine devices in women with AIDs.
- For most of the less frequent AIDs, there is virtually no information of the effect of hormonal contraception. This situation should be remedied.
- Information of how to counsel about contraception to women with AIDs is limited and hence should be expanded.

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