

ORIGINAL ARTICLES

Contraceptive practices in women with systemic lupus erythematosus and/or antiphospholipid syndrome: What advice should we be giving?

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Summary

Introduction. Systemic lupus erythematosus (SLE) is an autoimmune oestrogen-mediated disease. Antiphospholipid syndrome (APS) is an autoimmune acquired thrombophilia. These two conditions may co-exist and are most frequently diagnosed in young women. Hormonal contraception may promote lupus activity and thromboses. Medical practitioners may not know what advice to give these women regarding contraception.

Objectives. To determine the past and present contraceptive practices of women with SLE and/or APS, and to establish the incidence of complications related to use of various contraceptives. Also, the contraceptive information given to women following diagnosis was evaluated.

Study design. Observational questionnaire-based study of 86 women with SLE and/or APS attending the Lupus/Thrombophilia Clinics at St. Thomas' Hospital.

Results. One of the 19 (5%) women with SLE using the combined oral contraceptive pill (COCP) at the time of diagnosis reported a severe lupus 'flare'. Seven of the 32 (22%) women with APS using the COCP suffered from thromboses during use. There were no problems specific to women with SLE and/or APS using any other form of contraception. Thirty-nine (45%) women received no contraceptive information following their diagnosis, 37 (46%) were told to avoid the COCP due to the increase in lupus 'flare' and/or thromboses.

Conclusion. There is no clinically significant association between COCP use and lupus 'flare'. The high incidence of thromboses in women with APS using the COCP containing either second or third generation progestogens suggests that these women should be advised against using this form of contraception. Women with SLE and/or APS should be given more information about contraceptive issues.

Key words

antiphospholipid syndrome, contraception, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a non-organ specific autoimmune disorder affecting approximately one in 1000 people with a female to male ratio of 15:1 in the child-bearing years.¹ The aetiology remains obscure, but animal models suggest that hormonal factors may play a

Key message points

- Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) predominantly affect young women. Hormonal contraception, in particular the combined oral contraceptive pill (COCP), may exacerbate oestrogen-mediated lupus activity in SLE, and promote venous thromboembolism in APS.
- In the present study we found no evidence of increased lupus 'flare' in women with SLE using the COCP, but report a doubling of the background incidence of thrombosis in women with APS using the COCP. There were no unusual side effects with other forms of contraception in these women.
- Women with SLE and/or APS were either given no information regarding contraceptive practice or advised to avoid the COCP. We recommend that women with SLE are advised that they are not at increased risk of lupus 'flare' if they wish to continue using the COCP, whereas women with APS should be strongly advised against using the COCP.

key role in the pathogenesis of this condition^{2,3} and there are human data to support this.⁴ Some groups have reported an increase in frequency of lupus 'flares' during pregnancy which suggests that oestrogen is instrumental in mediating disease activity,⁵ but others have reported no exacerbation of disease in pregnancy.^{6,7} Hormones other than oestrogen have also been implicated in augmentation of SLE activity.⁸ Women diagnosed with SLE are often advised to discontinue the combined oral contraceptive pill (COCP),⁹ and the effect of oral contraceptives on the incidence and level of activity of SLE has been a focus of research for some years.^{10,11} Other methods of contraception may theoretically also pose problems. Little is known about the effect of progestogen-only preparations (PoP) in SLE, and with regard to barrier methods many women and their doctors are concerned that these may exacerbate the dermatological manifestations of the condition in some women, although there is no published evidence to support this. Use of intra-uterine contraceptive devices (IUCD) can cause problems because many women with SLE take steroid medication and might therefore be at increased risk of pelvic infection.

Antiphospholipid syndrome

The antiphospholipid syndrome (APS) is an autoimmune acquired thrombophilia predominantly affecting young women and it is classified as 'primary' if found alone, or 'secondary' if associated with SLE.¹² Although SLE and APS may co-exist in a group of patients, these are two quite

distinct diseases. The aetiology of APS is unknown, but the condition is characterised by elevated levels of lupus anticoagulant (LA) and anticardiolipin (aCL), antibodies which are overlapping subsets of antiphospholipid antibodies (aPL). Clinical features of APS are thromboses (arterial or venous), recurrent pregnancy loss and thrombocytopenia. Over the last few years there has been a great deal of interest in the association between COCP and thromboses in young women,¹³ and the type of progestogen seems to be particularly important in determining the incidence of venous thromboembolism.¹⁴ Third generation progestogen-containing preparations are considered most thrombogenic.¹⁵ Thromboses in young women using hormonal contraception often prompts investigation for underlying thrombophilias and many women with APS are diagnosed in this way.^{16,17} The background incidence of thromboses in young, non-pregnant women with APS without previous thromboses and not using any hormonal contraception is approximately 5% per patient year.^{18,19} Some groups report no increased incidence of thromboembolic disease in women with raised aPL taking low dose COCP.^{20,21} To our knowledge there is no information regarding the use of PoP in women with APS and the risk of thrombosis. Many APS patients with recurrent thrombotic events are treated with long-term oral anticoagulants and are advised against the use of IUCDs because of heavy bleeding.

Both SLE and APS predominantly affect young women and therefore giving appropriate contraceptive advice is important. In this observational study we determined the past and present contraceptive practices of women with SLE and/or APS and attempted to establish the incidence of complications related to use of various forms of contraceptive. We also asked women to comment on the information they received from medical practitioners regarding contraceptive issues following their diagnosis.

Method

Women between the ages of 16-45 years attending the lupus/thrombophilia clinics at St. Thomas' Hospital were invited to complete a confidential questionnaire. These women were classified into 3 groups - 1) SLE only, 2) APS only and 3) SLE and APS. SLE was defined according to the American Rheumatism Association Criteria.²² APS was defined as relevant clinical features in association with either aCL positive (IgG > 20 GPL or IgM > 6 MPL) or LA positive (a three stage test - dilute Russell viper venom test (DRVVT) ratio > 1.1, failure to correct prolonged coagulation with addition of normal platelet poor plasma,

and a confirmatory test demonstrating correction of prolonged coagulation upon addition of excess phospholipid). These tests were performed on at least two occasions over 6 weeks apart.

Results

There was an 83% response rate (86 women) in the 104 women approached, with 18 women refusing to take part in the study. The median age of non-participating women was 30 years (range 19-38 years). Reasons for declining to participate were no time after the consultation in seven cases, language problems in three cases, feeling too distressed (e.g. prior to recurrent miscarriage consultation) in another three cases, and not stated in the remaining five cases. Characteristics of women who did complete the questionnaires are shown in Table 1. The methods of contraception used at the time of the study are shown in Table 2. Methods of contraception used by the women prior to the diagnosis of SLE and/or APS are given in Table 3. Assessment of the information given to women following the diagnosis of their condition is shown in Table 4.

Group 1 - SLE only

This group had typical symptoms at the time of diagnosis of their condition with the majority presenting with arthralgia (Table 1). At the time of the study, nine (22%) women were not using any form of contraception, three were pregnant and four were trying to conceive. The most commonly used form of contraception was condoms in 18 (45%) women with no reported side-effects. Three (8%) women in this group were using COCP, one third generation progestogen-containing preparation, and two second generation progestogen-containing preparations, without any evidence of increased lupus activity. These results are summarised in Table 2.

Prior to the diagnosis of SLE, 25 (64%) women had used the COCP. In 14 (56%) of these cases a third generation progestogen-containing preparation was used, five (20%) had used second generation progestogen-containing preparations, and one woman had used Dianette® (ethinylloestradiol and cyproterone acetate). The remaining five (20%) women were unable to recall the type of COCP. Nine women were diagnosed with SLE whilst using the COCP, two discontinued the COCP due to lupus symptoms. One of these women reporting a mild 'flare' was using a third generation progestogen-containing preparation and the other was using Dianette® and reported a severe 'flare' after 2 months of use. The 'flare' resolved after discontinuation of Dianette®. Five other women discontinued

Table 1 Characteristics of women with SLE and/or APS

	GROUP 1 SLE only	GROUP 2 APS only	GROUP 3 SLE and APS
Number	39	30	17
Median age at time of study (years) (range)	31 (21 - 42)	31 (25 - 42)	30 (22 - 39)
Median age at diagnosis (years) (range)	25 (11 - 36)	30 (23 - 38)	25 (11 - 37)
Presenting symptoms	59% arthralgia 44% rash 10% lymphadenopathy 6% lethargy 6% alopecia 3% pleurisy 3% not stated	50% recurrent miscarriage 13% thrombosis on COCP 10% thrombosis not on COCP 10% Ix for stillbirth 7% thrombocytopenia 10% not stated	58% arthralgia 29% rash 18% alopecia 18% thrombosis on COCP 12% thrombocytopenia 12% haematuria

Table 2 Methods of contraception used at time of study

	GROUP 1 SLE only (n = 39)	GROUP 2 APS only (n = 30)	GROUP 3 SLE and APS (n = 17)
COCP	3 (8%)	2 (7%)	0 (0%)
PoP	1 (3%)	1 (3%)	1 (6%)
Depot	1 (3%)	0 (0%)	0 (0%)
Norplant®	0 (0%)	0 (0%)	0 (0%)
IUCD	1 (3%)	0 (0%)	1 (6%)
Mirena®	0 (0%)	0 (0%)	0 (0%)
Cap/Diaphragm	0 (0%)	1 (3%)	1 (6%)
Condom	18 (45%)	10 (34%)	7 (41%)
None	9 (22%)	9 (30%)	5 (29%)
Natural	5 (13%)	5 (17%)	2 (12%)
Sterilisation	1 (3%)	1 (3%)	0 (0%)
Other	0 (0%)	1 (3%)	0 (0%)

COCP	combined oral contraceptive pill
PoP	progestogen-only pill
Depot	intramuscular progestogen-only injectable
Norplant®	subdermal progestogen implant
IUCD	non-progestogen containing intra-uterine contraceptive device
Mirena®	progestogen-containing intra-uterine system
Sterilisation	refers to either female or male sterilisation

used of COCP for reasons unrelated to SLE: two complained of migraines, two had excessive weight gain and one developed phlebitis. In the SLE group, four (10%) women had used the PoP in the past, none reported any unusual side effects. Three (8%) women had used the IUCD previously, and one reported recurrent pelvic infection requiring oral antibiotics. Her IUCD had been removed 18 months prior to the diagnosis of SLE and before administration of steroid medication. These results are summarised in Table 3.

In 25 (64%) cases the diagnosis of SLE was made by hospital practitioners, mainly rheumatologists, but in one case it was diagnosed by a neurologist and in another by an ophthalmologist. Once the diagnosis was established, 21 (54%) women were given no information regarding contraception and none of these women changed their practice specifically because of their diagnosis of SLE. Eighteen (46%) of these women did get some contraceptive advice, in nine cases from their GP and the remainder from hospital doctors and family planning clinics. Fourteen

Table 3 Methods of contraception used prior to diagnosis of SLE and/or APS

	GROUP 1 SLE only (n = 39)	GROUP 2 APS only (n = 30)	GROUP 3 SLE and APS (n = 17)
COCP	25 (64%)	22 (73%)	10 (59%)
PoP	4 (10%)	2 (7%)	4 (24%)
Depot	1 (3%)	1 (3%)	3 (18%)
Norplant®	0 (0%)	0 (0%)	0 (0%)
IUCD	3 (8%)	3 (10%)	3 (18%)
Mirena®	0 (0%)	0 (0%)	0 (0%)
Cap / Diaphragm	3 (8%)	1 (3%)	0 (0%)
None	5 (13%)	3 (10%)	2 (12%)
Condom	16 (41%)	11 (37%)	8 (47%)
Natural	4 (10%)	3 (10%)	1 (6%)
Sterilisation	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)

COCP	combined oral contraceptive pill
PoP	progestogen-only pill
Depot	intramuscular progestogen-only injectable
Norplant®	subdermal progestogen implant
IUCD	non-progestogen containing intra-uterine contraceptive device
Mirena®	progestogen containing intra-uterine system
Sterilisation	refers to either female or male sterilisation

(36%) women were advised not to take the COCP due to the increased incidence of lupus activity, and three of these women were told that the PoP was a safer alternative. One woman was told that the only suitable types of contraception for her were condoms or natural methods. After completing the questionnaire, three (8%) women in this group requested more information about contraception during their consultation. These results are summarised in Table 4.

Table 4 Assessment of information regarding contraception given to women with SLE and/or APS

	GROUP 1 SLE only (n = 39)	GROUP 2 APS only (n = 30)	GROUP 3 SLE and APS (n = 17)
Given no information	21 (54%)	12 (40%)	6 (35%)
Told to avoid COCP	14 (36%)	14 (47%)	9 (53%)
Don't know / No response	4 (10%)	4 (13%)	2 (12%)
Requested more information	3 (8%)	2 (7%)	1 (6%)

Group 2 - APS only

In 15 (50%) of cases the diagnosis of APS was made following investigation for recurrent miscarriage and in three (10%) cases following investigation for stillbirth. Thromboses occurred in seven (23%) women with APS (five venous, two arterial), and four (13%) of these women were using the COCP at the time of the thrombotic episode (all venous) (Table 1). One had a right calf deep venous thrombosis (DVT) whilst using a third generation progestogen-containing COCP, the second had a left ileofemoral DVT whilst using a second generation progestogen-containing COCP, the third had a left calf DVT on a second generation progestogen-containing COCP, and the fourth had a pulmonary embolus whilst using a third generation progestogen-containing COCP. These reports were confirmed by review of patient case notes where available (four cases) and/or obtaining a clear history of treatment with a prolonged course of oral anticoagulants. None of these four women had additional risk factors for venous thromboembolism such as age > 35 years, overweight or smoking. All seven women with thromboses were advised not to use or to discontinue use of the COCP, and four were investigated immediately following the thrombotic episode and found to have APS. Another two women were diagnosed with APS within 2 years of their thrombotic event as a result of investigation for thrombocytopenia and a relative with a thrombosis, respectively. The remaining woman was only diagnosed 4 years later following investigation for recurrent miscarriage.

At the time of the study, two (7%) women with APS were using COCP, both second generation progestogen-containing preparations, with no reported side effects. Nine (30%) were not using any form of contraception and four of these were attempting to conceive. Ten (34%) women were using condoms, five (17%) used natural methods and one used an ovulation prediction kit. One woman in this group used PoP without reported side effects. These results are summarised in Table 2.

Prior to the diagnosis of APS, 22 (73%) of the 30 women had at some time used the COCP, in 11 (50%) cases third

generation progestogen-containing preparations, in seven (32%) cases second generation progestogen-containing preparations and unspecified in the remaining four cases. Six (27%) had discontinued the COCP for reasons unrelated to APS: one developed hypertension, two complained of mastalgia, another two complained of depression and mood swings, and one wished to conceive. The two (7%) women who had used PoP did not report any unusual side effects. One of the three (10%) women who had used the IUCD discontinued use due to heavy periods, but she was not taking anticoagulant medication. These results are summarised in Table 3.

In all cases hospital practitioners, mainly gynaecologists, rheumatologists and haematologists, made the diagnosis of APS. Twelve (40%) women were given no information regarding contraception following diagnosis, and this included the two women still using the COCP at the time of the study. Fourteen (47%) women were told to avoid the COCP because of the increased incidence of thromboses, in five cases by a gynaecologist, in four cases by their GP, and unspecified in the remaining five. One of these women had also been told to avoid the PoP for the same reason. After completing the questionnaire, two (7%) women in this group requested more information about contraception during their consultation. These results are summarised in Table 4.

Group 3 - SLE and APS

Most women in this group presented with SLE symptoms and subsequently developed clinical features of APS for which a 'lupus screen', which includes aCL and LA, was carried out (Table 1). Three (18%) women in this group developed thromboses whilst using the COCP. One woman who was known to have SLE developed an arterial cerebrovascular thrombosis whilst using a second generation progestogen-containing COCP and her symptoms were initially suspected to be related to lupus encephalitis. The other two women both had left calf DVTs. One was not known to have either SLE or APS at the time, and was unable to recall the type of COCP she was using, and the other was known to have SLE but not APS and was using a third generation progestogen-containing COCP. One woman in this group who had never used hormonal contraception developed a right calf DVT 2 years following diagnosis.

At the time of the study, none of the women with SLE and APS were using the COCP. One was using the PoP with no reported side effects. Another was using an IUCD without complications. Five (29%) women were not using any form of contraception, one of these was pregnant, another was attempting to conceive. Seven (41%) women were using barrier methods and two (12%) used natural methods. These results are summarised in Table 2.

Prior to the diagnosis of SLE and APS, 10 (59%) women had used the COCP, in six (60%) cases third generation progestogen-containing preparations, in one case a second generation progestogen-containing preparation, and unspecified in the remaining three cases. Four women were using the COCP at the time of diagnosis without reported increase in lupus activity. One had discontinued the COCP because of hypertension. Four (24%) women had used PoP without any complications, and all three (18%) Depot users had discontinued due to irregular bleeding. One of the three women who had used the IUCD discontinued due to heavy periods, but she was not taking any anticoagulant medication at the time. These results are summarised in Table 3.

In all 17 cases the diagnosis of SLE and APS was made by hospital practitioners, mainly rheumatologists. Six (35%) women were given no information regarding contraception and nine (53%) were told to avoid the COCP because of the increased incidence of lupus 'flare' and/or thromboses. In six (67%) cases this advice came from hospital doctors. After completing the questionnaire, one woman in this group requested more information about contraception during her consultation. These results are summarised in Table 4.

Discussion

Oestrogens are likely to play a significant role in the pathogenesis of SLE and several COCP are known to induce antinuclear antibodies.²³ Some studies have reported a high incidence of 'flare' in women taking these preparations,^{9,24} but this was not evident in our study. In the studies investigating the incidence of 'flare' in pregnancy, the background incidence of 'flare' in non-pregnant women not taking any hormonal medication (i.e. the control groups) is approximately 40% per patient-month.^{5,25} However, these studies were conducted in a hospital population and it is likely that the incidence of 'flare' is lower in women cared for predominantly by community practitioners, as they represent the less severe end of the disease spectrum. Whatever the true incidence of 'flare' in this population, our incidence of 5% in the COCP users is unlikely to be of clinical significance. Julkunen et al also found no increase in SLE activity in women taking COCP,¹⁶ and in a further study noted that women with SLE were less likely to use this type of contraception and more likely to opt for barrier and natural methods.¹⁸ These data are consistent with our findings. The women who were advised to discontinue or avoid use of the COCP invariably complied with this advice, so the numbers using barrier methods and natural methods may be a reflection of physician's advice as much as patient choice. PoPs did not seem to have any effect on SLE activity in our study, and other studies have shown similar findings.²⁶ As suggested by others,¹⁸ we found no problems with IUCD use and pelvic inflammatory disease in the present study.

The association between high dose oestrogen and venous thromboembolism has been recognised for several decades,²⁷ and some studies show that both oestrogens and progestogens are thought to be important in the pathogenesis of arterial thromboses too.²⁸ More recent studies, however, suggest that low-dose oestrogen preparations are *not* associated with an increased risk of arterial cerebrovascular disease,²⁹ and neither are second generation progestogen preparations.³⁰ Second generation progestogens are considered to have fewer adverse effects on coagulation mechanisms,³¹ whilst third generation progestogens have been shown to promote thromboembolic events.³²⁻³⁴ It seems reasonable, therefore, to assume that the incidence of thromboses in women using hormonal contraception is further increased if there is already a predisposition to thromboembolic disease, and in particular in women with underlying thrombophilias whether congenital or acquired. Some studies have shown that women with factor V Leiden mutation have an eight fold increase in the incidence of thromboses whilst using a second generation progestogen containing COCP compared to women with no underlying thrombophilia.³⁵ As stated previously, the background incidence of thromboses in non-pregnant women with APS without additional risk factors is approximately 5% per patient year.^{18,19} In the present study four of the 47 (9%) women with either primary or

secondary APS as the sole risk factor developed or presented with thromboses, and our slightly increased background incidence may reflect the particularly high risk population that attend this national referral unit. Nevertheless, the present study suggests that COCP use in women with APS more than doubles the background incidence of thrombosis, with seven out of 32 (22%) users affected. This is a clinically significant finding, even though the exact pathogenic mechanism by which COCPs promote thromboses is still unknown. With regard to other forms of contraception, the present study suggests that PoPs are not associated with any unusual side-effects, although very few women used this form of contraception. Barrier methods and natural methods were the most popular contraceptive practices in all three patient groups, suggesting that women with SLE and/or APS are keen to avoid hormone preparations of any kind, either as a result of advice given to them or through personal choice.

In the present study 39 (45%) women had received little or no information regarding contraception following the diagnosis of their condition. Two women with APS had continued to use the COCP, completely unaware of the potential hazards. Thirty-seven (43%) women were advised to avoid the COCP, but few were offered safer alternatives. Most of these women were under regular review by specialist hospital practitioners and some may have assumed that they would have been given relevant advice regarding contraception. Others may have perceived contraception issues are the remit of their community doctors and family planning clinics, and therefore the issue was not raised during their hospital consultations. Also, in the absence of evidence, some doctors may find it difficult to counsel women with any degree of certainty. Nevertheless, whatever the reasons for the deficiency in information given to these women, it is clear that the situation needs to be improved in order to minimise the incidence of potentially dangerous side effects in those who are at risk, and to reassure those who are not.

The relatively small number of women included in this study is in part due to the rarity of these two conditions, but also reflects the stringent inclusion criteria (see Methods) imposed. There is, of course, inherent bias in the results as the women invited to take part were attending hospital and therefore represent those with active disease. Also, as with all questionnaire-based studies, the information provided relies entirely on patient recall, which can be unreliable, especially with respect to distant events. Nevertheless, the data presented suggest that most forms of contraception are relatively safe for women with SLE. However, women with APS should be advised to avoid the COCP although other forms of contraception are not obviously associated with any unusual side effects.

Conclusion

In women with SLE alone, only one out of nine (11%) using the COCP at the time of diagnosis reported a significant 'flare'. These data suggest that the association with COCP use and lupus 'flare' is weak, if present at all, occurring in only one out of a total of 22 (5%) past and present users.

In women with primary or secondary APS there were seven thrombotic episodes in a total of 32 COCP users (22%), and this represents more than double the background risk of thromboses in non-pregnant women with APS without any additional risk factors. These data suggest that women with APS should be advised strongly

against using this form of contraception. This advice should apply to both second and third generation progestogen-containing preparations.

None of the women in any of the three study groups reported any unusual side effects with any other type of contraception.

Despite frequent review by medical practitioners, both community and hospital based, 39 of the 86 (45%) women in this study received no information regarding contraceptive practices following their diagnosis of SLE and / or APS. This is likely to be a reflection of the paucity of evidence-based information regarding the use of hormonal contraception in particular in these women. Provision of accurate information regarding contraceptive practice needs to be an integral part of the care of women with SLE and/or APS, and this study provides a guide for physicians in a position to give such advice.

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