

pregnancy on RA have been proposed, but a satisfactory explanation has yet to be established. The proposed mechanisms are summarised in several reviews^{1 3 22} and include the immunomodulating properties of female sex hormones, immunosuppression by the various pregnancy associated proteins—for example, α_2 glycoprotein, pregnancy induced suppression of the cell mediated immunity, and alterations in the glycosylation of IgG.²³ These mechanisms may also explain a postponement of RA onset to the postpartum period, but the difference in parity before disease onset is not so easily explained in this way. Some gradient in risk of RA with the number of pregnancies in parous women would be expected as a 'dose-response' in such biological mechanisms. If a common immunological dysfunction is responsible for infertility and subsequent development of RA this infertility should also be reflected in a smaller family size in women who later develop RA. Protection against RA by pregnancy but independent of the number of pregnancies may otherwise suggest a threshold mechanism. A tentative explanation might be that pregnancy, particularly early in life—as a radical immunological event—incites T cell repertoire changes resulting in 'vaccination' against RA.²⁴

When interpreting data on the divergence in parity between patients with RA and controls we must also consider that pregnancy is closely related to contraception and sexual life. Oral contraception probably protects against RA, but the lack of a dose-response relation and the many inconsistencies in the various studies have made it very difficult to find a plausible biological explanation.²⁵ The favourable effects of the oral contraceptive pill and pregnancy were found to be mutually independent,^{5 11} indicating that women who have either been pregnant or have used the oral contraceptive pill at some time in their lives are to a certain extent protected against the development of RA. Pregnancy and oral contraceptive use have in common that they both suppress ovulation. How suppression of ovulation might lead to a longlasting immunoprotection is as yet obscure. A further common feature of pregnancy and contraception is, in general, a sexually active life. Sexual lifestyle has not yet been considered as a study objective, except perhaps for a current survey of joint disease in nuns.²⁶ Sperm are potentially immunogenic and might incite changes in the immune system in sexually active women, particularly in the case of gastrointestinal (oral or anal) exposure to sperm.²⁷ On the other hand, sexually transmitted diseases may play a part by evoking some kind of immunisation against RA.

These hypotheses are still speculative, however, and we await further clues to the specific part that reproduction plays in the development of RA in women.

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Oral contraception and its possible protection against rheumatoid arthritis

Despite many epidemiological studies conducted in the search for environmental influences on rheumatoid arthritis (RA) we have few clues to possible risk factors. High hopes were raised following the publication of the Royal College of General Practitioners' oral contraception study, which provided evidence for a protection against RA among oral contraceptive users.¹ Many subsequent studies have been initiated to question this finding. A dozen years and numerous conflicting publications later we still seem to have

no clear answer to the question whether oral contraceptive use protects against RA or not.¹⁻¹³ The earlier studies had methodological problems, zealously discussed in international reports.¹⁴⁻¹⁶ Despite methodological improvements recent studies continue to fuel the controversy. To date seven studies have shown a reduction of RA of about 50% by oral contraceptive use,¹⁻⁷ whereas five studies reported no effect of oral contraceptive use on the development of RA⁸⁻¹² and one was inconclusive.¹³ In March 1989 a special

workshop on female sex hormones and RA was held in an attempt to reach a consensus among all the groups with a past or current interest in the field, the proceedings of which have been published.^{7 17-19 22 24} Two meta-analyses were presented, in which all reported relative risks of RA for ever users of the oral contraceptive pill were pooled. Each one reported a slight protective effect, with pooled estimates of relative risks of 0.73 (95% confidence interval (CI) 0.61 to 0.85)¹⁷ and 0.79 (95% CI 0.58 to 1.08).¹⁸ The preliminary confirmation of a protective effect of oral contraceptive use on the onset of RA by a methodological impressive study being conducted in Seattle⁷ supported the conclusion of the workshop that oral contraceptives probably have some association with RA.

We are still left, however, with several unsolved problems. How do we explain the discrepant results and what is the biological explanation for the oral contraceptive/RA association? Some of the meta-analyses performed on the various oral contraceptive studies nicely illustrate the possible explanations for the divergent results. Vandenbroucke *et al* using 'the odd man out' approach found it impossible to draw any common band between the results of the various studies simply because the confidence intervals did not overlap at all.¹⁹ The only way to pool the results was to follow an earlier suggestion by Valkenburg²⁰ and to separate the findings from the United States and those from Europe. Interpretation of the results in this way made it possible to draw a common band for the United States' studies set around a relative risk of 1, and a totally separate band for the European studies set around a relative risk of 0.5, which means a sizable protection against RA among oral contraceptive users in Europe. Spector approached the conflicting reports in his meta-analysis in a different way by pooling the risk ratios for hospital based studies and population based studies separately.¹⁷ The pooled risk ratio for the former was 0.49 (95% CI 0.39 to 0.63) compared with a pooled risk ratio of 0.95 (95% CI 0.78 to 1.16) for the latter. This implied a substantial protection of oral contraceptive use against RA needing specialist attention, as distinct from the absence of an effect of oral contraceptives on RA occurring in the population. At a close view this finding is not so different from the 'great transatlantic divide'¹⁹ as most of the European studies were hospital based. So patient selection may explain the divergence in the previous studies. A recent follow up study strengthens this explanation by finding that the negative association between oral contraceptive use before the onset of symptoms and RA was limited to patients with definite RA having a more severe disease course.²¹

These findings permit two hypotheses about how oral contraceptive use might protect against RA.

Firstly, the oral contraceptive pill may not protect against the development of RA, but rather may prevent the progression of mild to severe disease by modifying the disease process. There are some arguments against this hypothesis. All studies but one⁵ failed to find either dose or duration effects—short term oral contraceptive use and low oestrogen pills being as protective as long term oral contraceptive use and high dose pills. In addition, female sex hormones have been used therapeutically in an attempt to modify RA, but have shown only little beneficial effect on the course of the disease.^{22 23}

Secondly, the oral contraceptive pill may only prevent the development of the specific subgroup of RA characterised by progressive destructive arthritis and may not have a preventive effect on transient 'benign' RA. If it is assumed that HLA-DR4 is a marker for severe RA the fact that the protective effect of the oral contraceptive pill seemed to be similar in DR4 positive and DR4 negative women⁴ does not support this hypothesis.

An association between oral contraceptive use and RA is biologically plausible, but there are several potential explanations. In animal models reduction of incidence and improvement of experimentally induced polyarthritis by oestrogens has been described, but this differs according to the arthritis model and the species used.²⁴ It is uncertain which model is applicable to the human situation with RA. Reviews on the role of sex hormones in the immune system inform us that the interrelation between the immune system and the reproductive system is extremely complex.²⁵ Oestrogens, progestagens, and androgens can suppress the cell mediated immune response but probably not by way of the same lymphocyte populations. Conversely, oestrogens are stimulators of the humoral immune system, probably by inhibiting the activity of a suppressor T cell population. The ratio of oestrogens to androgens may determine whether the circulating hormones will be immunostimulatory or immunoinhibitory.²⁵ Most oral contraceptive pills not only consist of two hormones, but also contain varying doses of oestrogens and progestagens in different formulations. The balance between oestrogenic and androgenic properties may therefore vary considerably with consequently varying immunological effects.

Applying this laboratory knowledge to the reason why the oral contraceptive pill may prevent RA is not easy. Women, particularly women in their reproductive years, are more susceptible to RA than men. It is hard to reconcile this increased susceptibility at the time when endogenous female sex hormone levels are high with a possible protection against RA by exogenous female sex hormones. Likewise, the many inconsistencies even between the positive reports make it difficult to formulate a uniform explanation for the influence of oral contraceptive use on the development of RA. In 1978 the Royal College of General Practitioners' oral contraception study¹ showed that current users of oral contraceptives pre-eminently experienced a reduction in RA, which might be compatible with a direct immunosuppressive effect of the pill. Subsequent studies reporting a favourable effect of oral contraceptive use, however, failed to find a stronger effect in current users than in past users.^{2 4 13} Also, short term use seemed to be as effective as long term use, which suggests that a 'hit and run' effect independent of dose might be involved. It has been found that lines of T lymphocytes can induce or vaccinate against autoimmune arthritis,²⁶ and sex hormones might affect this T cell repertoire.

The most recent studies on the oral contraceptive pill and the risk of RA have merely added to the confusion. The Seattle study reported preliminary findings of a considerable reduction in the risk of RA in current users of oral contraceptives compared with only a slight reduction in past users.⁷ Conversely, analyses of the most recent data of the Royal College of General Practitioners' oral contraception study showed, in contrast with their 1978 finding, that the relative risk of RA among current users of oral contraceptive has now approached unity and approximates the risk among former users.¹² The disappearance of the contrast between current and former users seemed to result from a declining trend in the incidence of RA among former and never users of oral contraceptive but not among the current users. A tentative interpretation of this phenomenon might be that women who have never used the pill have nowadays taken on the same 'lifestyle' as pill users and are therefore experiencing the same protection against the development of RA.

It is increasingly being suggested that oral contraceptive use may in fact be a marker for some other causal factor which differs among the study subjects of the various studies. This idea has been supported by the inability to confirm Vandenbroucke's³ finding of a preventive effect of

non-contraceptive hormones on the development of RA.^{11 27} Aspects of behaviour related to oral contraceptive use which have been mentioned as possible risk factors include pregnancy, smoking and alcohol consumption, sexual behaviour, and recurrent genital tract infections. There is some evidence that pregnancy might be protective against the development of RA.^{5 28} Reports about a possible effect of smoking on the onset of RA are as conflicting as the reports on the oral contraceptive pill. In the studies where no protection by oral contraceptive use was found, no effect of smoking was found either,¹⁰⁻¹² whereas in one study reporting a favourable effect of the pill a protective effect of smoking and alcohol consumption was also suggested.²⁹ An aspect of lifestyle which has not been investigated yet is sexual behaviour and the risk of sexually transmitted diseases, though the apparent protection against RA among current users of oral contraceptives in Seattle seemed to be independent of the number of sex partners.⁷

Although differences in patient selection might explain the contrast between the positive and negative studies, the many inconsistencies, even in the positive studies, demand more knowledge about possible risk factors associated with the oral contraceptive pill before questions of the basic mechanisms can be considered.

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