PAPERS AND ORIGINALS

Use of Medroxyprogesterone Acetate as a Contraceptive in conjunction with Early Postpartum Rubella Vaccination

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Summary

During a 12-month period 170 women received early postpartum rubella vaccination. An injectable "depot" progestogen was given to each of these patients for contraceptive purposes at the same time as the vaccine was administered. Subsequent observations showed that the progestogen was effective as a contraceptive in this context and that it did not appear to affect the immune response of the patients to the vaccine.

Introduction

Rubella vaccination was introduced into the United Kingdom in 1970 with the recommendation that girls aged 11-14 years should be offered vaccine through the school health service and, later, that women employed in tasks which exposed them to rubella—for example, hospital staff and teachers—and women found to be susceptible to infection after serological examination should be vaccinated (Godber, 1970, 1972 a).

Though rubella vaccine strains have not been shown to be teratogenic they have occasionally been isolated from fetal material, and so might, in a certain number of cases, harm the fetus (Giles, 1972). There is thus a firm recommendation that no woman who is pregnant or might become so within two months of vaccination should be vaccinated. Such women must be considered for therapeutic abortion if pregnancy complicates vaccination. That this possibility is not remote was underlined by Mair and Buchan (1972), who reported that during 27 months from February 1970 six pregnancies had to be terminated in Leicestershire because vaccination had been performed in-

advertently during an early, undiagnosed pregnancy. During 1971 the Registrar General was notified of 43 pregnancies which had been terminated for the same reason (Registrar General, 1973). The majority of these women had not had their immune status determined before vaccination and it is probable that most of them were already immune. The vaccination and subsequent termination were unnecessary in these cases.

The Department of Health and Social Security (Godber, 1972 b) advised that rubella vaccine should be offered to women in the early postpartum period, as during the eight weeks after delivery they would be unlikely to conceive. This is generally true but can by no means be relied on and will vary with area and social class. Sharman (1966) showed that at least 25% of women ovulate within eight weeks after delivery. In 12 centres in America 5% of women having a second pregnancy within seven years of the first had become pregnant less than two months after delivery (Sever, 1971). A similar study in Oxfordshire of 700 women who had a second pregnancy within two years of the first showed that 1% of these had become pregnant less than two months after delivery (Baldwin and Freestone, 1971). Even this figure presents too high a risk and is a minimum one, as no information was available about the frequency of contraceptive use or of intercourse in the group studied. It would therefore be invaluable to have a reliable means of ensuring that women could not become pregnant within eight weeks of vaccination. Many countries, including the United States, South Africa, Sweden, and New Zealand, have had extensive experience in the use of medroxyprogesterone acetate in "depot" form as a long-term injectable contraceptive, and there is much literature on the subject (Jeppsson, 1972). The failure rate of this contraceptive is low (fewer than 0.1 pregnancy per 100 woman-years) if given regularly every three months (Powell and Seymour, 1971) and has been given safely in the postpartum period (Jones and Lonky, 1971).

Medroxyprogesterone appears to be a safe and effective contraceptive with minimum side effects even after repeated doses, does not need patient co-operation, and can be used in the immediate postpartum period. It thus seems ideal for use as a short-term, single-shot contraceptive to ensure that women given rubella vaccine do not become pregnant for the required two months after vaccination; D. P. Swartz (quoted by Cooper, 1971) used it for this purpose.

A trial of this contraceptive in women vaccinated postpartum has been conducted by us and the results are reported here.

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Patients, Materials and Methods

SELECTION AND FOLLOW-UP OF PATIENTS

Every patient who attended the antenatal booking clinic at the University Hospital of South Manchester was screened for rubella immunity in the Central Serological Laboratory (director, Dr. P. J. L. Sequeira). This was done by the haemagglutination inhibition (H.A.I.) test (Thompson and Tobin, 1970), and all women with a titre of 1/20 or less were regarded as suitable for vaccination (Tobin, 1973). Each woman thus identified, with the exception of those who had been listed for postpartum sterilization, was approached on either the first or second day of the puerperium and the details of the trial were explained to her, together with the possible implication of her lack of rubella immunity. The vaccine and progestogen were then offered, but it had previously been decided that if any patient objected to the contraceptive for whatever reason the vaccine alone would not be given. In fact, only five out of 175 patients declined to participate in the trial, four because they disliked injections and one for religious reasons; the remaining 170 women readily participated.

A specimen of blood was taken from each patient for rubella antibody estimation before the vaccination to confirm their immune status. As each vaccinee left hospital her general practitioner was notified of the vaccination in a standard letter, which also warned of the possibility of aberrant vaginal bleeding and suggested the prescribing of a cyclical oestrogen-progestogen pill if this became a problem, provided, or course, that there was no contraindication to such therapy. All these women were asked to attend the postnatal clinic six weeks later, and 146 (85.9%) complied with this request. On that occasion they were questioned about their symptoms and a further blood sample was taken for antibody estimation. Also at the postnatal clinic 100 other women who had not received either the vaccine or the progestogen were questioned in an identical manner using the same questionnaire.

A six-month follow-up survey was conducted in order to assess the efficacy of the contraceptive agent and its side effects. This was done by means of a carefully constructed questionnaire which was sent to the first 75 vaccinees and also to a control group of 75 randomly selected non-vaccinees who had been delivered during the same period. The response rates were 72% (54 out of 75) and 60% (45 out of 75) respectively.

VACCINES AND CONTRACEPTIVE

Cendehill (Cendevax) and RA27/3 (Almevax) rubella vaccines were used in the trial. The contraceptive progestogen used was medroxyprogesterone acetate (Depo-Provera) in a dose of 125 mg. The vaccine and progestogen were given from separate syringes via a single needle by deep intramuscular injection into the gluteal region.

LABORATORY TESTS

Rubella neutralizing and H.A.I. antibody titres were estimated by methods previously described (Hutchinson and Thompson, 1965; Thompson and Tobin, 1970), serum samples taken both before and after vaccination being tested together. Titres of 1/20 or more in the H.A.I. test and 1/4 or more in the neutralization test were taken as indicating the presence of antibody. In 37 instances where the presence of a low level of antibody was doubtful—for example, when the H.A.I. titre was less than 1/20 and neutralization titre was 1/4—the serum was screened at a dilution of 1/20 by the immunofluorescence technique for rubella-specific IgG antibody (Cradock-Watson *et al.*, 1972). Those vaccinees classed as “previously immune” had a positive reading in two or more of these tests. Cervical swabs for rubella virus culture in RK13 cells (MacDonald *et al.*, 1971) were

obtained from 72 of the vaccinees at their visit to the postnatal clinic. Platelet counts were also done on these patients at that time.

Results

SEROLOGICAL RESPONSE AFTER VACCINATION

Serological results were available for 133 women, 102 seronegative women and 31 previously immune women (tables I and II). Six weeks after vaccination a few patients had failed to produce neutralizing and H.A.I. antibody levels above the initial screening dilutions of 1/4 and 1/20 respectively (table I). Among these were four out of 54 who had Cendehill vaccine and one out of 48 who had RA27/3 who failed to react at all to the vaccine by that time, as judged by the lack of appearance of antibody in at least two of the three serological tests done on the sera of these patients. Three of the four Cendehill vaccinees were retested more than three months after vaccination and they were still negative at that time. The one who had failed to respond to RA27/3 even when retested at three months was born with a cataract in one eye, which was attributed to an attack of rubella during her mother's pregnancy, and it has been shown that congenital rubella can diminish or prevent response to vaccination (Cooper, 1971).

In the non-immune women the geometric mean titres six weeks after vaccination were higher after RA27/3 than after Cendehill (table I). The response after Cendehill, however, both in titre level and in the proportion of patients who seroconverted at six weeks, was comparable with the results of previous studies (MacDonald *et al.*, 1971). In those women who had a low level of antibody at the time of vaccination the proportion who responded to the two vaccines was similar, but the geometric mean H.A.I. titres after both vaccines were lower than those achieved in non-immune vaccinees (table II). Of the 18 immune patients producing a fourfold rise in the H.A.I. antibody titre 16 had prevaccination levels of this antibody of 1/20 or less.

TABLE I—Serological Response to Rubella Vaccination in 102 Non-immune Patients

Vaccine used	No. Vaccinated	No. Responding to:		Geometric Mean Titres			
				Before Vaccination		Six Weeks after Vaccination	
		Neutralization Titre >4	H.A.I. Titre >20	Neutralization	H.A.I.	Neutralization	H.A.I.
Cendehill	54	41	47	<4	<20	8	82
RA27/3	48	46	46	<4	<20	14	162

TABLE II—Serological Response to Rubella Vaccination in 31 Previously Immune Patients

Vaccine used	No. Vaccinated	No. with Fourfold Rise in:		Geometric Mean Titres			
				Before Vaccination		6 Weeks After Vaccination	
		Neutralization Titre	H.A.I. Titre	Neutralization	H.A.I.	Neutralization	H.A.I.
Cendehill	12	1	7	9	14	12	61
RA27/3	19	4	11	8	23	16	77

SIDE EFFECTS OF VACCINATION

The possible side effects of the rubella vaccines in the seronegative and the previously immune vaccinees compared with the control group of non-vaccinees are shown in table III. After RA27/3 three of the vaccinees developed mild clinical rubella

and one developed a painful arthritis of the knee and elbows. The percentage incidence of each individual symptom in the vaccinees, however, was no greater than that found in a previous trial with postpartum adults who had not received any concurrent progestogen therapy (MacDonald *et al.*, 1971). The 72 cervical swabs taken at the six-week postnatal clinic all failed to yield rubella virus; this was expected from previous experience (MacDonald *et al.*, 1971).

TABLE III—Incidence of Reactions in Rubella Vaccinees and Controls. Results expressed as Percentage of Patients

Symptoms	Cendehill		RA27/3		Control (n = 100)
	Immune (n = 12)	Non-immune (n = 54)	Immune (n = 19)	Non-immune (n = 48)	
Sore throat ..	17	20	16	21	15
Cervical lymphadenopathy ..	17	9	16	10	6
Fever ..	17	2	5	4	3
Rash ..	9	7	16	23	10
Headache ..	33	19	11	27	20
Arthralgia ..	0	2	0	6	3
Arthritis ..	0	2	5	4	1
Clinical rubella ..	0	0	0	6	0

EFFICACY AND ACCEPTABILITY OF CONTRACEPTIVE

The results given in table IV show that there was a significant difference between the vaccinees and the controls in all of the parameters considered. There was an obvious tendency for the duration of postpartum vaginal bleeding to be prolonged and the onset of menstruation delayed in some of the patients who were given the progestogen. There was no apparent effect on the regularity of the menstrual cycle once this had restarted. It transpired at the six-month follow-up that 33 of the 54 vaccinees (61%) compared with only 17 of the 45 controls (38%) had been prescribed a combined oestrogen-progestogen preparation either at the postnatal clinic or subsequently by their general practitioners. This difference almost certainly reflects the policy adopted whereby a combined oestrogen-progestogen pill was prescribed at the postnatal clinic for those vaccinees who were still experiencing troublesome vaginal bleeding as well as for those who requested such therapy solely for contraceptive reasons.

TABLE IV—Effects of Medroxyprogesterone Acetate on Vaginal Bleeding when administered during Early Postpartum Period

	Time in Weeks				Standard Error of Difference
	Vaccinees (n = 54)		Controls (n = 45)		
	Mean Interval	Standard Deviation	Mean Interval	Standard Deviation	
Confinement to first period ..	10.3	5.7	8.2	4.3	0.999
Confinement to regular menstrual cycle ..	14.4	7.6	11.2	5.2	1.293
Duration of postpartum vaginal bleeding ..	6.7	4.4	3.7	2.0	0.662

Four of the vaccinees were admitted for curettage 2, 6, 8, and 15 weeks respectively after delivery because of persistent vaginal bleeding. The first was due to retained placental tissue; no curettings were obtained from the second; the third yielded normal proliferative phase endometrium; and the fourth yielded a mixed secretory phase and proliferative phase endometrium. In the latter case the general practitioner had been prescribing an oral progestogen intermittently for six weeks. The curettage was corrective in all cases. Platelet counts were done on all the patients at the postnatal clinic and all were within normal limits, the range being 175,000 to 364,000/mm³.

Discussion

Postpartum rubella vaccination has already been well documented and the main purpose of this trial centred on the use of the contraceptive progestogen. Medroxyprogesterone acetate (6- α -methyl-17- α -acetoxyprogesterone) is a synthetic derivative of 17-acetoxyprogesterone. It appears to exert its contraceptive effect by means of a suppression of ovulation and, in common with most progestogens, by alteration of the cervical mucous. El-Mahgoub *et al.* (1972) showed that it had no significant effect on blood pressure or body weight or on the results of thyroid and liver function tests or intravenous glucose tolerance tests. The results of clinical trials of this drug have shown that it is an effective contraceptive agent with a fairly high incidence of aberrant vaginal bleeding, usually in the form of intermenstrual spotting or secondary amenorrhoea. Both are easily corrected by means of a single course of cyclical oestrogen therapy. The contraceptive effectiveness and the safety of this compound suggested that it would be suitable for use on a single-dose basis to cover early postpartum rubella vaccination.

The immune response to rubella vaccine and the reactions to it in this trial were comparable to those found previously in Manchester (Tobin, 1971), where vaccination was performed without the use of a "depot" progestogen. The percentage of non-responders and the geometric mean antibody titres of the vaccinees' sera were the same as those of a previous group tested six weeks after vaccination. Though some subjects would not have produced detectable antibody by then (MacDonald *et al.*, 1971) this interval had to be used in this trial because patients returned to the postnatal clinic at that time.

The earliest subsequent pregnancy in any of the vaccinees was conceived 17 weeks after confinement and vaccination, and was a planned pregnancy. Only 20 of the 146 vaccinees who were followed-up had resorted to additional contraception during the six weeks after confinement. Altogether 103 patients (70.5%) had had intercourse during that time. It may therefore be concluded that a single dose of 125 mg medroxyprogesterone acetate is an effective contraceptive agent within the context of this trial as, if 25% had ovulated, some pregnancies would have been expected among these 103 women.

The results show that the progestogen may prolong the duration of postpartum vaginal bleeding and delay the onset of the first menstrual period. This is not, however, regarded as a problem provided that the patients are warned of the possibility and their general practitioners advised accordingly. The short-term use of a cyclical oestrogen-progesterone preparation (preferably one with a low progestogen content) is sufficient to rectify any persistent vaginal bleeding due to the contraceptive, and unless there are other indications curettage need not be performed. Neither the progestogen nor the vaccine interfered with lactation in the small number of women involved.

Conclusion

Routine postpartum rubella vaccination of non-immune women with the concurrent administration of medroxyprogesterone acetate as a contraceptive agent is safe and effective. The procedure is now in routine use in the maternity unit at the University Hospital of South Manchester. The side effects are minimal and are acceptable, particularly when compared with the pregnancy risk associated with vaccination in the absence of reliable contraceptive cover. It may be that this procedure could be extended to include all non-immune women of childbearing age, but aberrant bleeding would presumably be more of a problem than it is in postpartum women.

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Incidence of Idiopathic Venous Thromboembolism in Nurses

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Summary

The incidence of idiopathic deep vein thrombosis and pulmonary embolism in a group of nurses (9.4 per 1,000 per year and 7.5 per 1,000 per year respectively) was much higher than the reported incidence in women of childbearing age in the general population (0.65 per 1,000 per year and 0.11 per 1,000 per year respectively). We suggest that these results show that nurses face an increased risk of idiopathic thromboembolism as a result of their occupation.

Introduction

Idiopathic venous thromboembolism is defined as that not associated with medical, surgical, or obstetric conditions, occurring in active, ambulant people without apparent cause (Hume *et al.*, 1970). Factors relevant in causation include ABO blood group (Jick *et al.*, 1969), body weight (Vessey and Doll, 1969), use of oral contraceptives containing oestrogen (McQueen, 1971), and possibly cigarette smoking (Frederiksen and Ravenholt, 1970; Sartwell *et al.*, 1969). Unusual physical effort has been implicated (Feinleib, 1972), but we have found no reference in the literature to occupational factors before the study of Sartwell *et al.* (1969) which found a high proportion of cases of idiopathic venous thromboembolism in a retrospective study to be nurses.

In a retrospective study of idiopathic venous thromboembolism in women of childbearing age we also noted that a proportion of cases were nurses, and have calculated the incidence of the disease in a defined population of nurses.

Materials and Methods

BACKGROUND

The initial aim of the study was to assess by a retrospective case-control method the effect of the advice from the Committee of Safety of Drugs (1970) that oral contraceptives containing more than 50 µg of oestrogen should not be prescribed. We attempted to identify all cases of idiopathic venous thromboembolism in women aged from 15 to 45 years diagnosed at this hospital between 1 January 1971 and 30 June 1973. Cases found had all been inpatients in the female general medical ward of 27 beds of which, on average, 80% are occupied by civilian patients.

CASE FINDING

Pulmonary Embolism.—Women patients with perfusion defects on lung scan during the relevant period were identified from the records of the Department of Nuclear Medicine, and the case notes of all the patients within the age group 15-45 years were retrieved. It is improbable that any case of pulmonary embolism was diagnosed without the aid of lung perfusion scanning.

Deep Vein Thrombosis.—Cases were identified from the ward admission book.

DIAGNOSTIC CRITERIA

Pulmonary Embolism.—The following criteria had to be satisfied: (1) lung scan—interpreted in conjunction with a chest x-ray picture, showing perfusion defects compatible with pulmonary embolism; (2) the consultant in charge had reached a diagnosis of pulmonary embolism; (3) rescrutiny did not cast doubt on diagnosis.

Deep Vein Thrombosis.—The following clinical criteria were applied: (1) agreement among attending clinicians; (2) three or more of the following—calf pain, calf tenderness, temperature difference between limbs, one centimetre difference in diameter between calves, pitting oedema; and (3) absence of any other condition to account for such signs. These criteria should yield a very low incidence of false positive diagnosis (Hicks, 1972).

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