Depo-Provera

Clinical Expert Report

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Introduction

Depomedroxyprogesterone acetate (Depo-Provera) is an injectable progestogen-only contraceptive. It differs from most other progestogen-only contraceptives in that it is a higher dose and acts primarily by inhibiting ovulation. In this, it is comparable to the combined oral contraceptive pill, but without containing oestrogen.

Despite the number and variety of contraceptives currently available, there is still no 'ideal' method. The characteristics of such an 'ideal' method could be said to be:

1. 100% safe (no health risks).
2. 100% effective
3. Independent of intercourse
4. Reversible
5. Free of unwanted side effects
6. Effective after an acceptable, simple and painless procedure
7. Not requiring continuous user motivation / memory
8. Cheap and easy to distribute
9. Independent of the medical profession
10. Acceptable to every culture, religion and political view
11. Used by or obviously visible to the woman, since she suffers the greatest consequences if the method fails or is omitted.
12. Not used by or obviously visible to the man, if religious or cultural reasons dictate confidentiality.

Nowadays, expectations of contraceptive methods are higher, and it would seem reasonable if a method actually had certain advantages such as:

1. Protection against sexually transmitted disease
2. Beneficial effects on women's health, for example
   - protection against gynaecological problems (such as fibroids, endometriosis, ectopic pregnancy)
   - relief from menstrual symptoms (such as menorrhagia, dysmenorrhoea, premenstrual syndrome)
   - reduction in the risk of gynaecological cancers

No contraceptive at present meets all these criteria. However, it is important to realise that couples have different requirements at various times of their lives. For example, efficacy may be of paramount importance to a young couple, who may therefore be willing to put up with some side effects or potential health risks in order to achieve their main goal. However, the same risk/benefit ratio may not apply to an older, more settled relationship, where concern about health risks may override those of efficacy. The assessment of risks and benefits will change throughout the lifetime of a woman or a couple, and needs to be reassessed at appropriate intervals. It is for this reason that a wide range of contraceptive methods are needed, allowing better 'tailoring' of contraception to suit individual needs.

Efficacy

The efficacy of Depo-Provera given in a dose of 150mg intramuscularly every 12 weeks is well established. Five large, controlled multicentre studies have been conducted, two sponsored by Upjohn (Protocols 144 and 148) and three by the WHO (WHO 1977, 1983, 1986) . These showed an in-use failure rate of 0.0 to 0.7 per 100 women-years. This makes Depo-Provera the most effective reversible contraceptive available, comparing favourably with the combined oral contraceptive pill, (in-use failure rates of 0.2 to 1.0 per 100 women-years), and also with the progestogen-only pill, (user failure rate 0.3 to 5.0 per 100 women-years (Fotherby 1989). Depo-Provera also appears to have greater efficacy than the other available injectable contraceptive, norethisterone oenanthate, whose failure rate ranges from 0.5 to 1.5 per 100 women-years (Fraser 1989).

An advantage of Depo-Provera over most other contraceptive methods is that the user failure rate approaches the method failure rate, because so little action is required of the user and also because intestinal upsets and most drug interactions are of no consequence. In addition, the failure rates at different ages are very similar, whereas for the progestogen-only pill the failure rate varies considerably with age, approaching one per hundred women years only by the age of 35 (Vessey et al. 1985). All methods which do not reliably inhibit ovulation show lower failure rates in older women, who are already less likely to ovulate and higher rates in those who are young and thus more fertile.

High efficacy is of great importance to women in certain special situations, such as partners of men awaiting vasectomy or for a vasectomy to be effective. or

those who are themselves awaiting sterilisation. Such women have decided that their family is complete and do not want an accidental pregnancy in the interim.

Reversibility

A woman cannot expect to conceive for three months after her last injection, this being the stated duration of action of the method. However, conception is often delayed for considerably longer, with a median delay in return of fertility of ten months, compared with only three months for combined oral contraceptive pill users and 4.5 months for IUD users. By about two years after discontinuation, cumulative conception rates (92-94%) are similar for the three methods.

It appears that the length of time for which DMPA has been used does not affect the rapidity with which fertility returns. Pardthaisong (1984) compared the return of fertility in 796 Thai women using DMPA with 437 combined pill users and 125 IUD users. Women were followed up for up to four years after they discontinued contraceptive use. DMPA users had a longer median delay to conception (5.5 months) than former combined pill (3 months) or IUD (4.5 months) users. Almost 70% of former DMPA users had conceived within the first 12 months following discontinuation and over 90% had conceived by 24 months. However, duration of use did not affect conception rates.

Recovery of fertility depends on circulating serum levels of DMPA and does not occur until these are very low or undetectable (Fotherby and Howard 1986).

The corollary of the delay in return of fertility is that there is some leeway in the timing of injections. The shortest period of time reported for return to fertility, as measured either by time to conception, time to ovulation, or serum DMPA levels, appears to be four months after the last injection. Thus there may be a 'grace period' of up to four weeks beyond the scheduled injection date, though two weeks may be considered a safer estimate.

Although a relatively long delay in return to fertility is a disadvantage of DMPA, this can be offset by appropriate counselling when a woman is considering the method. It is obviously not suitable for someone wishing to conceive within a year, but many women wish for longer term contraception and can plan a pregnancy in advance. In addition, this is unlikely to be a disadvantage to

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women who feel they have completed their family, but do not want the finality of sterilisation.

Side effects

Menstrual disturbance

This is undoubtedly the most troublesome side effect experienced with all progestogen-only methods, especially during the first few months of use. Approximately 40% of women on the progestogen-only pill experience irregular cycles, with a further 15% becoming amenorrhoeic (Fotherby 1989). The menstrual pattern in DMPA users is unpredictable, but is likely to consist of frequent light bleeding or spotting during the first few months of use. As duration of use increases, so does the frequency of amenorrhoea and after two years 70% of women are amenorrhoeic. Even by the end of one year 40% will be amenorrhoeic with another 40% having very infrequent, scanty bleeding. Amenorrhoea can be as worrying as frequent bleeding, and counselling about menstrual changes is of paramount importance. Studies have shown that discontinuation rates due to menstrual disturbance (including amenorrhoea) can be as high as 64.5% (Benagiano et al 1983) or as low as 5.3% (Basnayake et al 1984) with good counselling.

There are many cultural factors which affect tolerance of bleeding disturbance, and these must be taken into account. Women need to be warned about the possibility of frequent bleeding as this may disrupt their daily lives. Equally, many women feel that amenorrhoea is intrinsically unhealthy and need to be made to understand that regular menstruation is not a prerequisite for good health. Indeed, once this concept is understood, many prefer the freedom which amenorrhoea brings. It may be useful to explain that although they think they are having periods when taking the combined oral contraceptive pill, these are completely artificial and in reality they are amenorrhoeic but with induced withdrawal bleeds. It should be noted that tolerance of amenorrhoea, once understood, is likely to be higher in DMPA users than for the progestogen-only pill, because the possibility of unintended pregnancy with DMPA is extremely small. Progestogen-only pill users, on the other hand, are likely to worry that they may have missed a pill and in fact be pregnant (which is a real possibility).

For those in whom menstrual bleeding is reduced or absent (which will be the majority by the end of one year), DMPA actually protects against anaemia. In

addition, it has been suggested that it is the contraceptive of choice in homozygous sickle cell disease, since it has been shown to reduce the number of crises and improve the haematological picture (De Ceulaer et al 1982). There have also been anecdotal reports of an improvement in symptoms of premenstrual syndrome in DMPA users (Robinson & Broome, 1992, Cooper 1992).

Management of frequent or prolonged bleeding consists mainly of counselling and reducing the injection interval by as much as four weeks. Abnormally heavy or prolonged bleeding only occurs in 1-2% of women using the method. Regular oestrogen supplementation to control bleeding was common in the 1970s and early 1980s but appears to have no long-term advantage. Moreover, the use of oestrogen negates some of the advantages of using a progestogen-only method, introducing new health risks and side effects.

Although menstrual irregularity is a nuisance, with proper counselling the majority of women will tolerate it, especially when they know it is likely to improve long-term.

Weight gain

More than 70% of women gain weight on DMPA, a fact which may limit its acceptability in Western countries. Approximately 10% of women show no change in weight, while 20-25% lose weight. The increase appears to be due to deposition of fat rather than fluid retention. Studies show that the mean weight gain after one year is usually about 2kg, increasing with continued use to 9kg after 5.5 years of use. In the WHO study (1986) approximately 2% of women discontinued the method because of weight gain: this percentage is likely to be higher in Western countries where women are under much greater pressure to be slim.

It has been hypothesised (Liskin 1983) that DMPA stimulates the hypothalamic appetite control centre in the brain, causing women to eat more than they would otherwise. If this is the case, counselling about food intake while using DMPA may help prevent excessive weight gain.

No studies appear to have looked specifically at weight changes in women who have ceased to use DMPA. However, an unpublished study looking at bone density changes (Cundy et al, preliminary report) noted that women stopping DMPA showed a significant reduction in mean body weight of 2kg, whereas body

weight increased in women continuing DMPA and was unchanged in control subjects.

CNS effects

The most frequently reported CNS effect is headache, but this appears to occur with approximately the same frequency as in users of the combined oral contraceptive pill and IUDs.

Effects on bone density

Studies of oestradiol levels in DMPA users have shown similar levels to those in the early follicular phase of normally cycling women and above those in postmenopausal women (Jeppsson et al 1982 and Mishel et al 1972).

A recent study (Cundy et al 1991) has highlighted the issue of potential osteoporosis in long term DMPA users. The effect of DMPA on lumbar spine and femoral neck bone density (as measured by dual energy x ray absorptiometry) was evaluated in 30 premenopausal women who had been using DMPA for 5 to 20 years, (median 10 years). All the women were currently using DMPA and all were amenorrhoeic. Thirty premenopausal women matched for age, race and body mass index served as one control group, and 30 postmenopausal women with similar matching (apart from age) served as another control group. However, significantly more women in the DMPA group than in either of the control groups were current cigarette smokers ($p< 0.01$), and neither duration of smoking nor amount smoked were taken into account. When matching for current smoking status was performed, nine pairs had to be eliminated, leaving only 21 pairs for comparison.

Bone density in the lumbar spine was significantly lower in the DMPA group than in the premenopausal control group (6.8%, $p = 0.013$) as was bone density in the femoral neck (6.7%, $p = 0.028$). DMPA users had significantly higher bone densities in both the lumbar spine and femoral neck than matched postmenopausal controls (8.9%, $p = 0.001$, and 4.0%, $p = 0.04$ respectively).

Serum oestradiol measurements showed a mean of 81 pmol/L in the DMPA group, which was significantly higher than in the postmenopausal group,(mean serum concentration 34 pmol/L). Oestradiol measurements were not available for the premenopausal group, but would be assumed to be over 100 pmol/L.

The reductions in bone density found in this study would not have placed the DMPA users at current risk of fracture. The study design has been criticised (Hinchley 1991, Szarewski & Guillebaud 1991, Lane 1991) for inadequate matching of cases and controls, the lack of bone density measurements prior to commencement of DMPA (it is possible that the DMPA group simply started off at a disadvantage and showed no change following commencement of the contraceptive), and possible overmatching for body mass index, given that DMPA is known to cause weight gain (this artificial weight gain may not be associated with higher bone density as would be the case in women of a naturally heavier weight).

This is the only study to date which has specifically investigated possible effects of DMPA on bone density, and cannot be considered conclusive. This is an area in which prospective, properly designed studies are urgently required, not just in DMPA users, but also for users of low dose progestogen-only methods who are amenorrhoeic. Such women also cease to ovulate and therefore could theoretically be at risk of oestrogen deficiency.

Cundy et al (1992) have carried out a second study, of which only preliminary results are currently available. In this study, which again has no measurements of bone density in women prior to commencement of DMPA, 17 never-users of DMPA were compared with 22 ongoing DMPA users and 13 women who discontinued DMPA. Of the 13, one had a hysterectomy very shortly after stopping the drug (for unconnected reasons) and it is therefore questionable whether the authors should have included her in the comparison.

Once again, DMPA users and ex-users were more likely to smoke than the controls. It was noted that the ex-users lost weight after stopping DMPA. No details are given of the ex-users current contraception, except that one commenced the combined oral contraceptive pill and was thus taking oestrogen.

The ex-users showed a significant increase in lumbar spine bone mineral density a median 12 months after stopping DMPA (range 9 to 20 months).

The authors suggest that the apparent reversibility of the bone density changes supports the hypothesis that DMPA can cause bone loss. However, the very small numbers and relatively short term follow up still result in a need for a properly designed, larger prospective study before any conclusions can be drawn.

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Following the decision of the United States FDA to grant DMPA a licence, Upjohn have agreed to set up a long-term study over five years to investigate this effect.

Metabolic effects

Since the data in this area are often contradictory and methodology varies greatly between studies, I have asked [redacted] to review the studies in this field. [redacted] report is provided in full as an appendix to mine: here I shall briefly summarise the most important points.

In general, studies looking at the effect of DMPA on metabolic parameters are confusing due to differing methodology, inadequate matching of cases and controls, lack of appropriate comparison groups and a paucity of data regarding Caucasian women. All this limits the conclusions which can be drawn, apart from an obvious need for modern, properly designed studies.

Most studies do not show significant changes in total cholesterol or triglycerides. However, some studies (Kremer et al 1980, Deslypere et al 1985, Fahmy et al 1991a, Enk et al 1992) have shown reductions in HDL cholesterol of between 15 and 20%. This is similar to changes observed in studies of combined oral contraceptive pills containing progestogens such as levonorgestrel (Godsland et al 1990). Although no prospective study has shown that lowering HDL cholesterol increases the risk of cardiovascular disease, it is generally held that this is a possibility and that preparations causing the least change in lipid levels are to be preferred (Consensus Development Meeting, 1990).

In the UK, the newest combined pill formulations, containing progestogens such as desogestrel, gestodene and norgestimate do not cause any lowering of HDL cholesterol levels (Godsland et al, 1990, Robinson et al, 1990). In this respect, unless modern, well controlled studies of the effects of DMPA on lipids show less effect on HDL, such pills may be considered to have an advantage over DMPA for women at increased risk of cardiovascular disease.

With respect to carbohydrate metabolism, the data appear relatively consistent, although there have been no studies of Caucasian women in the last 15 years. At contraceptive doses, DMPA has been shown to impair the oral glucose tolerance test (OGTT) glucose response and to increase the insulin response. Although it is difficult to make comparisons, the changes appear to be of approximately the same order of magnitude as those seen with the combined oral contraceptive pill.

Thus, although development of overt diabetes in previously normal subjects has not emerged as a problem, DMPA should preferably be avoided in diabetics and women with a history of gestational diabetes.

DMPA does not appear to have any significant effect on haemostasis, although again, there is a lack of modern data . In this respect, DMPA has an advantage over the combined oral contraceptive pill.

Effects on blood pressure

DMPA does not appear to have any significant effect on blood pressure. The great majority of studies show minor fluctuations in blood pressure, which are not consistent or significant (Black et al 1979, Schwallie & Assenzo 1973, WHO 1983, 1986). In this, it is similar to the progestogen-only pill. In contrast, the combined pill has a tendency to cause some increase in blood pressure (Gillmer M 1989). Thus, DMPA may be preferable to the combined pill in women who have a tendency to hypertension.

Breast Cancer

The issue of cancer risk in DMPA users has been perhaps the most controversial and damaging in its history. Early studies in beagles suggested that DMPA users could be at higher risk of breast cancer, but it was later found that the beagle dog is an inappropriate model for the human (FDA, Sobel 1991).

The most recent publication, from the long term WHO study (1991) has been reassuring in this respect. This study reported data on 869 cases of breast cancer and 11,890 controls. 109 (12.5%) of the cases and 1452 (12.2%) of the matched controls were DMPA users. The relative risk of breast cancer in DMPA ever users was 1.21 overall (95% CI 0.96 - 1.52). The relative risk was raised only in women who were under 35 years at diagnosis, but there was no trend in increasing risk with duration of use. On the contrary, there was a marginally significant reduction in risk with increasing duration of use for women over the age of 35. Risk was in fact greatest within three months of the first injection, which is difficult to explain in biological terms, and introduces the possibility of surveillance bias. The authors of the report also put forward the suggestion that it is possible that DMPA unmasks tumours which would have presented later. They also comment that the suggested increase in risk (relative risk 1.4, 95% CI 0.88-2.22) is small and of the same order of magnitude as that in studies of the

combined oral contraceptive pill. The same WHO group found a relative risk of 1.26, (95% CI 0.95-1.66) for users of the oral contraceptive pill in this age group (WHO 1990). The UKNCC (1989) study of pill users also showed a relative risk of 1.43 (95% CI 0.97-2.12) for up to eight years of use and a relative risk of 1.74 (95% CI 1.15-2.62) for more than eight years of use. In this context, it is perhaps interesting to note that, as mentioned before, oestrogen supplementation was regularly used in the 1970s and early 1980s particularly in Thailand: thus, many women in this study, as in others, would have in effect been using a combined oestrogen - progestogen preparation for varying amounts of time, with DMPA as the progestogen. Since the same WHO group found a difference in risk of endometrial cancer between ever users and never users of concurrent oestrogen, it would be interesting to know if such a difference also exists for breast cancer (Szarewski and Guillebaud, 1991). Such an analysis has not yet been published.

A recent case-control study from New Zealand (Paul et al, 1989) found no overall increase in the risk of breast cancer, but a slight increase in risk in women between the ages of 25 and 34, though the number of cases under 35 who had used Depo-Provera for at least two years was very small.

Since 1980 five other studies have looked at breast cancer risk: one showing a slight increase in risk (Lee 1987), the others no increase (Higgins 1985, Ory 1984, Liang 1983, Greenspan 1980). These studies suffer from methodological flaws (by the authors' own admission) and/or very small numbers, thus they have effectively been superseded by the WHO study.

Endometrial cancer

Concern was initially raised regarding the possibility of an increase in risk of endometrial cancer in DMPA users when two of 12 rhesus monkeys receiving 50 times the human dose developed endometrial carcinoma (Fraser and Holck 1983).

Data from the WHO study (1991) are reassuring in this respect. The report included data on 122 women with endometrial cancer and 939 controls. Three cases and 84 matched controls were DMPA users, giving a relative risk of 0.21 (95% CI 0.06 - 0.79). The authors comment that all three cases had received oestrogen premenopausally. No DMPA users who had not used concurrent oestrogens developed endometrial cancer. Although the numbers were small,

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there was a suggestion that the protective effect of DMPA appeared to last for at least eight years after cessation of use.

These results are similar to those of many studies of the combined oral contraceptive pill, which has been shown to roughly halve the risk in users. In addition the CASH study (1987) showed that the protective effect persisted for 15 years after stopping the combined pill.

There are no published data which show an increase in the risk of endometrial cancer in DMPA users.

Ovarian cancer

The WHO study (1991) found no increase in the risk of ovarian cancer in DMPA users, with a relative risk of 1.07 (95% CI 0.6 - 1.8). The report included data on 224 cases and 1781 matched controls. No consistent patterns of increasing or decreasing risk were noted according to duration of use, time since first or most recent use or age at first use of DMPA.

The authors point out that, since in Thailand DMPA has generally not been given to nulliparous women, the study is unable to comment on risk in nulliparous women, who are a high risk group for ovarian cancer.

It is well documented that the combined oral contraceptive pill provides a roughly 40% reduction in the risk of ovarian cancer in users, the effect lasting for at least 15 years after cessation of use (CASH 1987). The authors speculate that such an effect would be plausible in DMPA users, but that this study would not have had the power to detect it.

There are no other adequate studies assessing the risk of DMPA on ovarian cancer, but the WHO study, while of limited power, is reassuring in this respect.

Cervical cancer

Studies looking at the risk of cervical cancer and contraceptive use are notoriously difficult to interpret because of the link between contraception and sexual behaviour, which is itself a risk factor for the disease.

A study from Costa Rica (Oberle 1988) combined cases of invasive cancer with carcinoma in situ, (a preinvasive lesion nowadays referred to as cervical intraepithelial neoplasia grade 3 or CIN 3). The study showed no overall increase in the risk of cervical cancer or carcinoma in situ (relative risks 1.1, 95% CI 0.6 - 1.8 and 1.4, 95% CI 0.6 - 3.1 respectively), but was limited by small numbers (only 10 cases of cervical cancer in DMPA users compared with 40 controls).

A multi-centre Latin American study of 759 cases and 1467 age matched controls (Herrero 1990) reported an increased risk in long term users (more than five years) of DMPA and Norethisterone oenanthate. There were 11 cases and 16 controls in this group, with a relative risk of 2.4 (95% CI 1.0 - 5.7). Overall there was no increase in risk (RR 0.8, 95% CI 0.5 - 1.2). In view of the small numbers and the much larger WHO study it is unlikely that the observed increased risk in long term users is real.

The WHO study (1992) reported data from 2,009 cases and 9,583 controls. Some information was obtained in the later stages of the study (from 1984) on smoking habits and history of papillomavirus infection. The relative risk of invasive squamous cell carcinoma in women who had ever used DMPA was 1.11 (95% CI 0.96 - 1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed. This is the largest and methodologically most sound study carried out to date and provides reassurance that DMPA use does not alter the risk of invasive squamous cell cervical cancer.

Liver cancer

The WHO study (1991) is the only study to report on the risk of liver cancer in DMPA users. Data from two countries, Kenya and Thailand, were presented, with 71 cases and 530 controls. In both countries Hepatitis B is endemic. The relative risk was 1.64 (95% CI 0.4 - 6.6) in Kenya and 0.33 (95% CI 0.1 - 1.0) in Thailand. No consistent changes in risk were observed with duration of use, time since last use or time since first use. The authors comment that the data from Kenya are unreliable since there the majority of tumour diagnoses were made on clinical grounds alone, without histological confirmation. In contrast, in Thailand 86% of cases were histologically confirmed.

While limited by small numbers and the unreliability of data from Kenya, this study suggests that it is unlikely that DMPA has any significant effect on liver cancer in Hepatitis B endemic areas.

Overall conclusions regarding cancer risk

The WHO studies have greatly improved our knowledge of DMPA and the risk of cancer. They are the largest studies to date, independent and well designed. No significant overall increase has been reported for breast, cervix, ovarian or liver cancer. A protective effect has been shown for endometrial cancer, similar to that of the combined oral contraceptive pill. For breast cancer there is a suggestion that the risk may be slightly increased in young women: the magnitude of this increase is similar to that reported for the combined oral contraceptive pill in this group (UKNCC, 1989). In absolute terms, this means that cumulatively, 0.05% of women taking Depo-Provera under the age of 35 might develop breast cancer as a result of their use of the method.

The current data are reassuring. However, it would be useful for further long term studies to be carried out in Western countries. This is an area in which post-marketing surveys could be set up, especially now that DMPA has been licensed by the FDA, greatly increasing the potential number of Western users.

In utero exposure

Some controversy surrounds two recent reports by the same investigators concerning in utero exposure to DMPA in relation to outcome of pregnancy and survival during infancy (Pardthaisong 1991, Gray 1991).

The studies were carried out in the northern Thai province of Chiang Mai, where there has been extensive use of DMPA since the 1960s. In both studies, there were essentially four groups of women: 830 cases of accidental pregnancy in DMPA users, 743 cases in which DMPA was given to an already pregnant woman, 601 accidental pregnancies in combined oral contraceptive (OC) users and 2578 planned pregnancies in which the foetus was not exposed to steroid contraceptives. There were 1431 infants born to DMPA treated mothers, 565 born to OC users and 2307 infants in the control group.

The authors noted that the sociodemographic characteristics and behaviour of the DMPA group placed them at a higher risk for adverse pregnancy outcomes than the mothers in the OC and control groups. Mothers in the DMPA group were significantly older, or higher parity, of lower socio-economic status and less educated than those in the OC and control groups. They were also more likely to

be involved in agricultural work, to smoke and drink during their pregnancies and to deliver at home. They were less likely to have received antenatal care. Their mean weight and height were significantly lower than those of mothers in the control group.

No differences were observed in the rates of stillbirths, ectopic, molar or multiple pregnancies.

The odds ratio (adjusted for most sociodemographic variables) for low birth weight was increased for foetal exposure to DMPA in both the accidental pregnancy and the already pregnant DMPA groups (1.4, 95% CI 1.0 - 1.8 and 1.7, 95% CI 1.3 - 2.2 respectively). The risk was also increased for accidental pregnancies in OC users (1.5, 95% CI 1.2 - 2.0). The authors conclude that the increased risk in OC users is likely to be due to self selection since the pregnancies were all unplanned. They also suggest that the already pregnant DMPA group was self selected for poor outcome since these women may have deliberately used DMPA, thinking that it would cause abortion.

For foetal exposure to DMPA due to accidental pregnancy, there was a significant trend of greater risk for conceptions occurring within four weeks of injection, decreasing as the injection to conception interval increased. As a result, the authors postulate that high levels of DMPA (such as are found in the first four weeks after injection) may have an adverse effect on birth weight in infants exposed during that time.

It has been pointed out (Hogue 1991) that a serious limitation of this observation is the fact that conception dates were estimated by nurses either by using the date of the last menstrual bleed, or from the uterine size. In DMPA users, where bleeding episodes are often very irregular (and bear no relation to ovulation) and amenorrhoea is common, estimates based on the last menstrual bleed may be inaccurate, certainly by a couple of weeks. In addition, since medical records were only available for 55% of the infants in the DMPA group, this estimate in many cases had to be made during the interview, several years later. None of the Gray and Pardthaisong papers (1988, 1991, 1992) make it clear how the estimate of uterine size was in fact obtained. Since it is extremely unlikely that ultrasonography was available, it can be assumed that a clinical measurement was made, either by abdominal palpation or by estimation of fundal height. Such measurements can have widely varying degrees of accuracy, depending on the method used, and none are considered to be precise (Altman and Hytten, 1989).

In their second study, Pardthaisong and Gray (1991, (b)) compared survival during infancy for children born to these groups of mothers. The children exposed in utero to DMPA had higher neonatal and infant mortality rates (44.3 and 62.9 per 1000 live births, respectively) than did the controls (19.8 and 29.1 per 1000 live births). Mortality in infants exposed to OCs was intermediate between that in the other two groups. Adjustment by logistic regression showed no significantly increased risk of mortality among infants exposed to OCs, but the odds ratio for death was significantly increased with DMPA exposures due to accidental pregnancy (1.8, 95% CI 1.1 - 3.0 for neonatal death and 2.0, 95% CI 1.3 - 3.2 for infant death). Adjustment for low birth weight reduced the risks and the authors therefore suggest that low birth weight may act as an intermediate determinant of DMPA associated mortality. Once again, the greatest effect was seen in infants exposed to DMPA within four weeks of an injection. However, the comments regarding the estimation of time of conception made earlier apply also to this study.

It is interesting to compare the results of the recent studies with those of an earlier study by the same investigators (Pardthaisong & Gray, 1988). In this study, all babies born in a hospital in Chiang Mai between July 1975 and January 1978 were examined and medical records gathered shortly after delivery. There were 4023 women who had used no contraception before the index pregnancy, 1229 who had used DMPA and 3038 who had used OCs prior to or during the pregnancy.

In their description of the methods used, the authors comment on the difficulty of estimating the time between last contraceptive use and conception in the DMPA users. Women could often not recall the date of their last bleed and some were amenorrhoeic. Therefore, the interval from last contraceptive use to date of delivery was used, and in the analysis, date of conception was estimated from delivery date minus 9 months. Although the study cannot be compared with the 1991 data, the difficulties of estimating the time of conception are highlighted here.

This study found a significantly higher frequency of low birthweight among infants of nonusers of contraception compared to ex pill users. The frequency of low birthweight in ex DMPA users was intermediate between these two groups. Once again, DMPA users were older and of higher parity than those in the OC and nonuser groups.

The study was particularly concerned with congenital defects, and there was a suggestion, although inconclusive, that DMPA users might be slightly more likely to have infants with polysyndactyly and chromosomal defects. However, the authors conclude that in view of the unrelated nature of these defects, the distant preconceptual exposure to DMPA and the possibility of chance effects due to multiple comparisons, a causal association is in fact unlikely.

Several other studies have looked at the effects of oral MPA or low dose weekly DMPA given during pregnancy for the treatment of threatened abortion (Yovich et al 1988, Katz et al 1985, Rawlings et al 1963). Although these may not be entirely comparable with the effects of DMPA 150mg, none of the studies showed any significant difference in congenital abnormalities between infants exposed to MPA/DMPA and the controls.

Long term effects of in utero exposure on progeny

Jaffe et al (1988, 1989, 1990) in Israel has published a series of studies looking at the effects of oral MPA and DMPA (analysed together) on children exposed in utero. The children were followed up for 17 years in a double blind prospective study: the mothers were unaware of the specific aims of the study, which was presented in the form of a general questionnaire on long term growth and development in children related to events in pregnancy. 74 teenage boys and 98 teenage girls who were exposed in utero to MPA were compared with 385 teenage boys and 448 teenage girls who were not exposed. After adjustment for social factors, there were no significant differences between the two groups in terms of general health, growth, sexual development, intellectual development and sex-dimorphic traits and behaviour (aggression, physical activity levels and sex role identity).

Pardthaisong and Gray (1992) have reported on the long-term growth and development (up to age 15) of the children already described in their previous two studies (1991 (a) and (b)). There were several types of exposure: only in utero, only via breast milk, both in utero and via breast milk, and a control group of non-exposed children. The total size of the DMPA exposed group was 1215, while the control group contained 1167 children.

They found no difference in weight or height between the control children and the DMPA exposed children (for any type of exposure). There were also no

differences between the groups with respect to onset of puberty, apart from a report (not confirmed by examination) of slightly delayed appearance of pubic hair in DMPA exposed girls.

This study is reassuring in that it is relatively large and shows no significant adverse effects on long term growth and development in DMPA exposed children.

No other studies have been large enough to give meaningful results.

Overall conclusions on in utero exposure

Most studies to date do not show any adverse effects on infants or children exposed in utero to MPA or DMPA. The data are more difficult to interpret with respect to DMPA since more relate to oral MPA exposure during weeks five to eighteen (on average) of pregnancy than to DMPA 150mg exposure in early pregnancy.

Two recent reports by Pardthaisong and Gray suggest there may be an increased likelihood of low birth weight, resulting in an increased risk of neonatal and infant death in infants exposed to DMPA within four weeks of conception. These studies have been much criticised, as discussed earlier, and cannot be viewed as conclusive. Nevertheless, they should be noted and further studies are required, particularly in the West. In this country, the combined neonatal and infant mortality rate is 8/1000 live births (OPCS 1990), much lower than that quoted for Chiang Mai. Also, obstetric, paediatric and community services are much better than in rural areas of Thailand. Thus, even if DMPA exposed infants were at slightly greater risk of low birth weight, firstly, the number of such cases would be extremely small because the method is so effective, and secondly the risk of adverse sequelae would probably be reduced due to better standards and availability of care. However, until further data are available, the importance of avoiding accidental exposure in pregnancy (by giving the initial injection within the first five days of a period and by checking that women who are overdue for an injection by more than two weeks are not at risk of pregnancy) should be stressed.

It is however, reassuring to note that studies, including a continuation of Pardthaisong and Gray's study, do not show any adverse effects on long term growth and development in DMPA exposed children.

Effects on lactation and nursing infants

Women who are breast feeding, although at slightly reduced risk of pregnancy, still need contraception. The combined oral contraceptive pill has been shown to reduce milk production, and is therefore not advised for lactating women (Hull V. 1981).

In contrast, progestogen-only methods do not suppress lactation, and indeed, DMPA has been shown to prolong the duration of lactation (Schwallie 1981), and in some studies to increase the quantity of breast milk (Koetsawang 1977, WHO 1988).

The composition of breast milk does not appear to be appreciably altered by DMPA, whereas use of the combined oral contraceptive pill may cause a significant decrease in total energy content and widespread changes in milk constituents (WHO 1988). The progestogen-only pill, like DMPA, does not suppress lactation or alter the composition of the breast milk (Fotherby 1989).

Serum levels of DMPA are highest within the first four weeks after injection, and the quantity of hormone transferred to the infant is correspondingly highest during this time. However, studies looking at the children of mothers who breast fed while on DMPA (whether commencing DMPA immediately after delivery or after four weeks) have shown no adverse effects on either short term or long term growth and development (WHO 1988, Koetsawang 1972 and 1984, Dahlberg 1982, Jimenez 1991). However, to minimise the amount of hormone the infant initially receives, and in view of the increased tendency to irregular bleeding if DMPA is given within the first four weeks after delivery, it would seem sensible, where possible, to delay the first injection until at least the fourth week postpartum. An increase in bleeding irregularities has also been demonstrated in women using the progestogen-only pill immediately postpartum (Fotherby 1989). The serum and milk hormone levels of progestogen-only pill (POP) users are lower than those of DMPA users: however, the very exact timing of pill taking required by POP users offsets this advantage in many women.

Lactating mothers who require contraception have a more limited choice of method than the general population, because the combined oral contraceptive pill suppresses lactation and alters the composition of breast milk. If they do not want to use a barrier method (which is also less effective), their choice is restricted to the progestogen-only pill or injectable progestogens, such as DMPA.

Neither method adversely affects lactation nor the composition of breast milk. Both are associated with an increase in menstrual irregularity if given within the first four weeks postpartum. The progestogen-only pill has the advantage over DMPA of being a lower dose and thus less hormone passes into the milk. On the other hand, studies do not suggest that the higher dose of DMPA adversely affects growth and development of the infant. Many women find the strict time-keeping required of POP users to be extremely inconvenient and difficult: this applies at least as much to lactating women whose lifestyle is disrupted by the baby. Thus, for a proportion of lactating women DMPA potentially offers an effective, simple and acceptable method of contraception.

Discussion

As mentioned previously, all currently available contraceptive methods have drawbacks, although these will vary in importance to different couples. DMPA has many of the characteristics proposed for an 'ideal' contraceptive method. It approaches 100% user efficacy, in which it is rivalled only by the combined oral contraceptive pill. All other reversible methods have higher failure rates, especially in young women, where user failure rates for the progestogen-only pill (POP) are quoted as approximately 4 per hundred women years, while user failure rates for barrier methods are as high as 15 per hundred women years (Sherris, Moore & Fox, 1984). Intrauterine devices vary, but average use failure rates quoted are between 2 and 4 per hundred women years: however, IUDs are not generally recommended for young, nulliparous women because of the risk of pelvic inflammatory disease.

Use of DMPA is independent of intercourse and also independent of the user's memory (and thus of continuing motivation), other than remembering the 12 weekly appointments. For many women this is a great advantage. Oral contraceptive methods involve remembering to take a pill each day, in the case of the progestogen only pill, within the same three hours each day. This places considerable strain on women who lead irregular lifestyles, who are very busy or travel frequently. Such women often describe a constant 'fear of forgetting', especially with the POP. Barrier methods mostly require action at the time of intercourse, reducing their acceptability to many couples, and contributing to the user failure rate, when the method is simply forgotten in the heat of the moment. Diaphragms are often well tolerated by cohabiting couples, but otherwise may be inconvenient for women to have to carry around. IUDs are convenient from the point of view of ease of use, but in young women

particularly the fitting procedure is relatively complicated and the risks of pelvic inflammatory disease are greater. For certain women, DMPA offers the advantage of not requiring storage and not being obvious in use, enabling them to maintain secrecy about their use of contraception. Nevertheless, since it is a method used by women, it offers the peace of mind of knowing that it has indeed been used.

The injection itself is more acceptable since the present 1ml formulation was introduced - the former 3ml injection was more uncomfortable. There are women who do not like injections, but there are also women who do not like taking tablets or who do not like vaginal methods.

DMPA is reversible, albeit with a longer delay than other methods. This is a disadvantage to couples seeking short term contraception, for whom the method is therefore unsuitable. However, many women want long term effective contraception and do not view this as a drawback. Counselling about the delay is important so that when couples are planning a pregnancy they are aware that they will need to make decisions about stopping contraception earlier than with other methods.

The main potential disadvantages of DMPA in this country are likely to be menstrual disturbance and weight gain. The combined oral contraceptive pill gives the appearance of excellent cycle control because it removes the natural cycle altogether and replaces it with an artificial one. All progestogen-only methods, whether low or high dose, lead to menstrual disturbances, so in this respect, DMPA is not unique. Counselling about this aspect is of the utmost importance, since continuation rates vary so dramatically depending on the quality of counselling. The probability of achieving amenorrhoea on DMPA is higher than for other progestogen-only methods, and may be an advantage to some women, who can understand that it is not dangerous and welcome the freedom which amenorrhoea brings. In addition, certain women will benefit from an improvement in symptoms such as dysmenorrhoea, menorrhagia (and therefore anaemia) and premenstrual syndrome. Indeed, sufferers of sickle cell disease have been shown to benefit from a decreased number of crises and improved haematological picture.

Although troublesome, the menstrual disturbances which occur in DMPA users very rarely require operative medical intervention, and can often be improved simply by short courses of oestrogen or shorter injection intervals. (However,

long term oestrogen supplementation is not recommended, as mentioned on Page 5). Again, women need to know what can be done so that they are aware that they should seek advice early, rather than miserably waiting for their twelve week appointment.

The possibility of weight gain is likely to be a deterrent for some women: we live in a society in which it is considered attractive to be slim, and many women spend a great deal of time and effort dieting. However, there will be those who are not unduly concerned about the possibility of moderate weight gain, and those in whom the other advantages for them make it worthwhile to try the method. In this respect, the progestogen-only pill has the advantage over DMPA in not being associated with weight gain. Modern combined oral contraceptive pills do not usually cause weight gain: in this context, it is interesting to note that many women expect to gain weight on the pill, and yet opt to use it because of its other advantages - this may be encouraging regarding the potential acceptability of DMPA.

Like the combined oral contraceptive pill, DMPA offers protection against ectopic pregnancy and is sometimes used in the palliation of symptoms of endometriosis (since it induces amenorrhoea). Also like the combined pill, it may offer protection against pelvic inflammatory disease, because of the effect of progestogen on cervical mucus. This would make it a better choice than the intrauterine contraceptive device for young women who are forgetful pill takers and may be at risk of sexually transmitted disease.

With regard to cancer risks, the latest evidence is generally reassuring. As for the combined oral contraceptive pill, although no overall increase in the risk of breast cancer has been demonstrated, there is doubt regarding the possibility of a small increase in risk in young women. However, the risk does not appear to be any greater than that suggested for the oral contraceptive pill. No increase in risk has been demonstrated for ovarian, cervical or liver cancer, and a five fold protective effect has been found for endometrial cancer. Again, the data are remarkably similar to those described for the combined oral contraceptive pill, and it has been suggested that a reduction in risk of ovarian cancer (as found in OC users) may yet be demonstrated. Although non-hormonal methods of contraception have not been shown to be associated with any increase in cancer risk, it should be remembered that they also do not show any protective effects and are also usually less effective.

DMPA has no appreciable effects on blood pressure or thrombosis risk. In this it has an advantage over the combined oral contraceptive pill, and provides a simple, effective alternative for women who cannot use the pill for these reasons. Similarly, it has been suggested that women who suffer from focal migraine and are therefore advised against use of the combined oral contraceptive pill can still use progestogen-only contraceptives (Luscombe H, 1992). Although the POP is medically safe in these circumstances, in young women it is less effective, and involves strict time keeping, which will be disadvantages for some women.

The effects of DMPA on carbohydrate metabolism appear to be not unlike those seen with the combined oral contraceptive pill, and therefore its use, like that of the pill, is limited in diabetics and those women with a history of gestational diabetes. For such women the progestogen-only pill has always been a valuable option.

Judging by currently available data, DMPA appears to cause a lowering of HDL cholesterol of approximately the same magnitude as that seen with older combined oral contraceptive pills. Although this has not been proven to increase the risk of cardiovascular disease, the newest combined pills do not cause such a lowering: thus they may have an advantage over DMPA in women who are at increased risk of cardiovascular disease.

In lactating women, progestogen-only methods have a clear advantage over the combined oral contraceptive, which is contraindicated because it causes suppression of lactation and substantially alters the composition of breast milk. Although the POP is a lower dose than DMPA there is no evidence to suggest that use of DMPA has a deleterious effect on the growth or development of infants.

The remaining areas of concern are the issues of bone density and in utero exposure. With regard to bone density, there is at present insufficient evidence of any deleterious effect, but further studies are required to resolve the issue. Studies are also required in users of the progestogen-only pill, since in theory, amenorrhoeic POP users could be at risk since they cease to ovulate. In the interim, the possibility of bone density scanning in long term DMPA users who are approaching the menopause should be considered. Where this is unavailable, an indicator may be the serum oestradiol level. For some women approaching the menopause, the addition of replacement oestrogen could be considered, since

DMPA itself would provide the necessary progestogenic protection against endometrial cancer, while also being contraceptive.

Two recent studies have suggested that there may be an increase in the risk of low birth weight and neonatal and infant death in babies exposed to DMPA within the first four weeks of conception. This has not been shown in previous studies and some doubt exists over the validity of the findings. Further studies are required. In particular, there is a lack of data from Western countries, where the combination of the high efficacy of DMPA, much lower neonatal and infant death rates and higher standards of obstetric and neonatal care may result in different conclusions.

Perhaps the most important issue surrounding the use of DMPA is that of patient information. The method has had a particularly bad public image, which naturally makes potential users anxious and subject to misinformation from poorly informed or biased sources. Also, it is temporarily irreversible during its three month duration, so the duration of any problems or anxieties resulting from side effects may be longer than for other methods. It is of paramount importance that easily understood, accurate patient information leaflets are available, since biased and inaccurate information is readily available from women's magazines, perpetuating the myths surrounding the method. The proposed data sheet recommends that women should be given the company leaflet: I believe that any new licence should also include such a proviso regarding the revised leaflet proposed by the company. When the general public's (and medical profession's) level of knowledge is improved, it may no longer be necessary for a legal requirement to exist, but I believe as an interim measure it would be very useful.

In summary, DMPA is a contraceptive method which would be a valuable option to some women, probably mainly those who, for either medical or social/domestic reasons, cannot or do not want to use the combined oral contraceptive pill but still wish for a very effective method of contraception. Like all methods, it has certain drawbacks, but these do not appear to be more serious than those of other available methods. There are still some unanswered questions regarding long term effects, but such uncertainties also exist for other methods currently in use. DMPA would be a useful addition to the range of contraceptives currently available for general use.

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