Contraceptive failure of Depo-Provera®: long-acting reversible contraceptive (LARC) methods do fail too

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Case report

A 28-year-old woman, gravida 4 para 1, presented to primary care for contraception. Following discussion she opted for the progestogen-only injectable, Depo-Provera®. Her first injection was given on Day 5 of her cycle and she had not had any unprotected sexual intercourse that cycle. The injection was given into the dorso-gluteal muscle by the practice nurse who had experience of giving intramuscular (IM) injections. The woman attended the surgery 13 weeks later, having missed her appointment the previous week. She was given a second injection – again by an experienced practice nurse – into the gluteal muscle. No other precautions were advised. It is not documented in the case notes whether the patient was counselled that this injection was outside the product license.

The patient re-presented with symptoms of nausea 6 weeks following her second Depo-Provera injection. A pregnancy test was positive. A dating ultrasound scan was arranged. This took place 7 weeks after her second Depo-Provera injection and showed a viable pregnancy at 9 weeks 2 days estimated gestation, indicating that conception would have occurred around the time of the second injection. The patient opted for a termination of pregnancy and had a copper-bearing intrauterine device fitted at the time of abortion.

The case was reported to the manufacturer of Depo-Provera. They carried out tests on both injection batches, which showed satisfactory medroxyprogesterone concentrations.

The patient was in good health, a non-smoker and had not taken any recent medication. Her weight was 68.0 kg at the time of the first injection and 71.3 kg at the time of the second. On discussion with the patient it transpired that she had three previous unplanned pregnancies. The first occurred while she was not using any contraception and resulted in a therapeutic abortion. Her next two pregnancies occurred whilst taking the combined oral contraceptive pill. The patient reported taking St John's wort when she became pregnant on the second occasion but no clear cause for contraceptive failure was found to have led to her third pregnancy.

The authors obtained written informed consent from the patient concerned and showed her a copy of the manuscript.

Discussion

According to the latest figures from the Office of National Statistics, an estimated 3% of women aged 16–49 years are using injectable contraception in the UK.[1]

J Fam Plann Reprod Health Care 2009; **35**(1): 59–60
(Accepted 13 November 2008)

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The failure or pregnancy rate of Depo-Provera is quoted by the National Institute for Health and Clinical Excellence (NICE) as 0.4% (4 in 1000 over 2 years) when given at *licensed dosage intervals* of 12 weeks.[2]

The UK Electronic Medicines Compendium and the manufacturer's patient information leaflet state that if the interval from the preceding injection is greater than 89 days (12 weeks 5 days), women should be advised to use additional contraceptive measures for 14 days after this subsequent injection.[3] However, according to NICE and the Faculty of Sexual and Reproductive Healthcare (FSRH) *UK Selected Practice Recommendations* (UKSPR), women attending up to 2 weeks late for repeat injections may be given the injection without the need for additional precautions.[4] This use is outside the UK marketing authorisation. Informed consent is needed when using Depo-Provera outside licensed indications and FSRH guidance suggests that this is discussed with the patient and documented in the case notes.

Potential reasons for failure of Depo-Provera include delayed injections, incorrect administration and, rarely, drug interaction. Aminoglutethimide (an inhibitor of adrenocorticosteroid synthesis, and not currently available in the UK) may significantly depress the bioavailability of Depo-Provera when administered concurrently.[3] However, liver enzyme-inducing medications are *not* thought to significantly affect the kinetics of medroxyprogesterone acetate and therefore neither dosage nor interval between doses needs alteration. In the present case, the injection was given beyond the manufacturer's recommended interval for administration but well within current FSRH guidelines. The patient was not taking any other medication so the possibility of drug interaction can be ruled out.

Advice regarding administration contained within the Summary of Product Characteristics (SPC) for Depo-Provera recommends "care that the injection is given into the muscle". The site is "preferably the dorso-gluteal muscle; but the deltoid may also be used". However, since there is a preparation of medroxyprogesterone that may be given subcutaneously and at a lower dose, this would seem an unlikely cause of failure.

Depot medroxyprogesterone acetate (DMPA) is an aqueous suspension available in a pre-filled syringe, which should be thoroughly mixed before use to ensure complete suspension of the contents. If this were not done, could this contribute to inappropriate absorption of the drug? In addition, some medication manufacturers advise against massaging the site after injection as it reduces the effect of the medication by dispersing it too readily. We checked the SPC for Depo-Provera and found no warnings against this practice.

Finally, when performing IM injections the 'Z-track technique' is commonly used to prevent any drug from leaking out of the muscle. This technique involves pulling the skin to one side of the injection site; the needle is then held at 90 degrees to the skin and penetrated into the muscle. The plunger is pulled back to observe for blood aspiration, and if no blood is aspirated then the drug is slowly and continuously injected. The needle is then withdrawn at the same angle at which it went in and the skin released. This has the effect of breaking the needle track as the skin and subcutaneous layers move back over

the muscle and the drug is locked within the muscle. If this technique is not used there is the possibility that the drug may have tracked out.

These suggestions seem unlikely culprits for the failure of Depo-Provera in the present case. It is important to remember that even with perfect use failures may still occur, and the possibility of pregnancy should be considered in women presenting with symptoms that are suspicious of pregnancy. Despite the low failure rates quoted by NICE, there is additional research that suggests higher failure rates for Depo-Provera of up to 7% with typical use.[5] Delay in diagnosing an unplanned pregnancy could result in delay in seeking an abortion should the pregnancy remain unwanted. This would have important health implications for the woman in terms of increased complications and implications for the provider in terms of cost.

It is also worth emphasising that the routine interval for administration of Depo-Provera remains at 12 weeks and women should be encouraged to attend for their repeat injections at the correct time. Where the injection is given beyond the manufacturer's recommended and licensed dosage interval of 12 weeks 5 days and unprotected sexual intercourse has occurred, should health professionals be doing a check pregnancy test at 3 weeks (in order to avoid delay in making the diagnosis) and suggesting additional contraceptive precautions for 7 days? Current FSRH and NICE guidance do not make this recommendation but it may be worth considering in certain groups of women.

Statements on funding and competing interests

Funding None identified.
Competing interests None identified.

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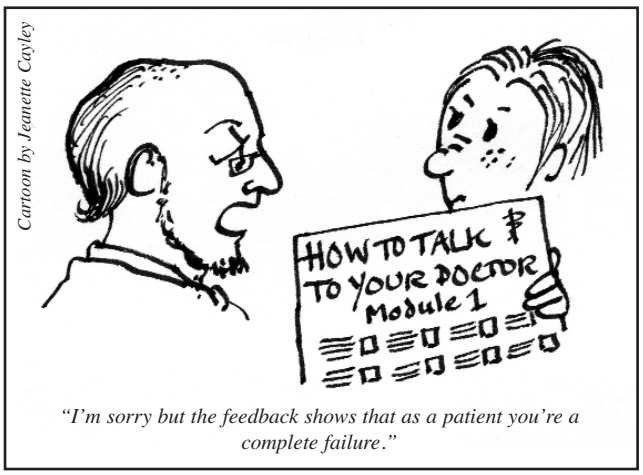

"I'm sorry but the feedback shows that as a patient you're a complete failure."