

# Early contraceptive failure of Implanon® in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz

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## Case report

We present the case of a 23-year-old nulliparous woman who had Implanon® inserted in February 2003 for the purpose of long-term contraception. She was diagnosed HIV-1 antibody positive in March 2004 and was on zidovudine 600 mg, lamivudine 300 mg and efavirenz 600 mg daily. She was also a known asthmatic with regular use of a Becotide® inhaler.

The patient was a general practitioner referral in August 2005 to the local emergency department with a suspected diagnosis of retrocaecal appendicitis following a 12-hour history of right iliac fossa (RIF) pain.

The pain was worsening and was unresponsive to self-medicated Nurofen®. There was associated nausea but no vomiting. The patient had experienced post-Implanon amenorrhoea until January 2005 when she resumed regular 3-day periods in 28-day regular cycles. She had never had a smear test. She was in a stable relationship with an HIV-positive boyfriend.

Initial examination in the emergency department showed her to be well perfused and haemodynamically stable with normal vital signs. The main findings were in the abdominal area where she had RIF tenderness with no guarding or rebound. There were no palpable masses and there were no clinical signs of peritonism or ascites.

A clinical diagnosis of ectopic pregnancy was entertained as a result of a positive pregnancy test whilst other test results were awaited. Her pain was controlled with regular analgesia. Her haemoglobin level was 9.1 g/dl, white cell count  $10.8 \times 10^9/l$ , C-reactive protein 6 mg/l and her electrolyte and urea levels were all normal.

An initial abdominal ultrasound scan in the emergency department before referral to the gynaecology on-call team was reported as follows: "Free fluid is seen throughout the abdomen. In the RIF, there is a  $10 \times 10 \times 10$  cm heterogeneous mass, which appears separate from the uterus. The ovaries are not clearly seen. The liver, spleen, pancreas, kidneys are normal". The report suggested differential diagnosis of a complex ovarian cyst, an ectopic pregnancy or an appendiceal mass.

On admission by our team (gynaecology) the patient's clinical condition remained unchanged. The implant was palpable on the inside of her left upper arm. She still had mild tenderness in the RIF. An ectopic pregnancy was thought unlikely in view of the earlier ultrasound report

and a decision was made to observe the patient overnight provided she remained haemodynamically stable. A repeat departmental scan the next morning reported "a right adnexal mass measuring  $26 \times 21 \times 31$  mm with a gestational sac plus a viable fetal pole with a crown-rump length of 8 mm compatible with a gestation of 6 weeks and 1 day". The earlier reported cyst on the right ovary was not seen. There was extensive fluid in the upper abdomen, suggestive of a ruptured ectopic pregnancy. The serum  $\beta$ -human chorionic gonadotrophin result was 26 679 IU/l and the haemoglobin level in the morning was 7.1 g/dl. An exploratory laparotomy confirmed the diagnosis and the patient made a good recovery following surgery.

## Discussion

Organon International first introduced Implanon in the UK in September 1999. Its website states that "Implanon® is a single-rod contraceptive implant that is inserted under the skin of the upper arm and provides highly reliable protection against pregnancy for up to 3 years". This case is presented in order to highlight the fact that this statement in terms of effective duration of use may not be applicable in HIV-positive women on antiretroviral medication.

Implanon contains 68 mg of a synthetic progestogen, etonogestrel. The implant releases approximately 40  $\mu$ g etonogestrel per day, which inhibits ovulation by suppressing the luteinising hormone surge; increases the viscosity of cervical mucus, reducing sperm penetration and motility; and provides effective contraception for 3 years. Implanon is absolutely contraindicated in the presence of severe liver disease, and long-term use of liver enzyme-inducing drugs can reduce efficacy.<sup>1</sup>

Following its introduction to the market, several early studies suggested a 100% contraceptive effectiveness of Implanon by means of ovulation suppression. One study demonstrated that the first ovulation with Implanon was after about 30 months of use.<sup>2</sup> A recent cohort study of Implanon users in a real-life setting in Luton, UK reported a contraceptive effectiveness of 100% for 3 years of use in their study population.<sup>3</sup>

Contraceptive failures are now well reported in the literature. Most of the contraceptive failures have been attributed to insertion technique error (i.e. implant not found when pregnancy has been diagnosed), failure of contraceptive effect secondary to its association with an enzyme-inducing drug and untimely insertion (i.e. insertion after Day 5 of the menstrual cycle or in women who are already pregnant at the time of insertion).<sup>4</sup>

In a postmarketing case series of more than 218 unintended pregnancies associated with Implanon in the first 3 years following its launch in Australia, the authors reported an approximate failure rate of 1 in 1000 insertions.<sup>5</sup> The most common reason for contraceptive failure was insertion failure. Other reasons included unknown pregnancy at the time of insertion, incorrect timing of insertion, expulsion, and interaction with hepatic enzyme-inducing medication.

The implant in the present case was clearly palpable and intact, thereby ruling out insertion technique error, breakage, expulsion, incorrect timing of insertion and

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unknown pregnancy at time of insertion as potential causes of contraceptive failure. The only explanation for contraceptive failure in the present case would appear to be the hepatic enzyme-inducing effect of the antiretroviral therapy, since the patient was not on any other medication apart from a Becotide inhaler for her asthma.

Efavirenz is the only component of the patient's antiretroviral regimen known to have a liver enzyme-inducing effect. The nucleoside reverse transcriptase inhibitors are metabolised via a different route and thus would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Efavirenz has a high affinity for binding to plasma proteins, displays a prolonged plasma half-life, is metabolised via cytochrome P450 2B6 and 3A4, and induces CYP450 activity during chronic administration.<sup>6</sup> Other compounds that are substrates of CYP3A4 such as progesterone, anticonvulsants and anti-tuberculosis agents may have decreased plasma concentrations when co-administered with efavirenz. Dosage adjustment is therefore necessary with the co-administered drug. Efavirenz is also known to increase the plasma concentration of ethinylestradiol, the clinical significance of which is not known.<sup>7</sup>

## Conclusions

HIV-seropositive women continue to be sexually active after diagnosis. All such women should be counselled regarding proper use and possible side effects of their chosen method(s) of contraception.

The importance of using barrier methods in addition to their primary choice of contraception cannot be overemphasised – even in those women with HIV-positive partners – in order to reduce the potential for transmission of drug-resistant virus. Condoms should be promoted and provided free of charge, since their correct and consistent use during sexual intercourse decreases the risk of transmitting HIV to the uninfected partner by up to 96% in addition to providing protection against other sexually transmitted infections and unplanned pregnancies.<sup>8</sup>

All such women wishing to use hormonal contraceptive methods should also be given condoms and counselled as to their use, especially since protease inhibitors, rifamycins and non-nucleoside reverse transcriptase inhibitors may decrease the effectiveness of hormonal contraceptives.<sup>7,9,10</sup>

## Statements on funding and competing interests

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### CLINICAL CONUNDRUM CORRESPONDENTS

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## ERRATUM

### 'Migraine and use of combined hormonal contraceptives: a clinical review',

E Anne MacGregor, *J Fam Plann Reprod Health Care* 2007; **33**(3): 159–169

Readers should be aware that the text heading in Box 1 on page 166 was incorrectly printed as *1.1 Migraine without aura*, when in fact the heading should have been *1.2 Migraine with aura*. The correct version of Box 1 is reproduced below.

#### Box 1: International Headache Society (IHS) diagnostic criteria for typical aura with migraine headache<sup>84</sup>

Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than 1 hour, a mix of positive and negative features and complete reversibility characterise the aura, which is associated with a headache fulfilling the criteria for '1.1 Migraine without aura'.

#### 1.2 Migraine with aura

##### Diagnostic criteria:

- A. At least two attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
  1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)
  2. Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
  3. Fully reversible dysphasic speech disturbance
- C. At least two of the following:
  1. Homonymous visual symptoms<sup>1</sup> and/or unilateral sensory symptoms
  2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
  3. Each symptom lasts ≥5 and <60 minutes
- D. Headache fulfilling criteria B–D for '1.1 Migraine without aura' begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder