Ectopic pregnancy with Implanon®

Patricia M N Henderson, Morven D Gillespie

Case report

A 25-year-old, non-smoking woman, para 2+0, presented at our family planning clinic complaining of having experienced intermittent pelvic pain over the previous 2 weeks. She reported 7 weeks of amenorrhoea, of feeling pregnant, and stated that two home pregnancy tests had tested positive. She had had an Implanon® inserted 28 months previously and this was easily palpable at the clinic. A pregnancy test done in the clinic was negative. The patient wished to have her implant removed and arrangements were made for this to be done 9 days later. The patient re-presented the following day having done two further home pregnancy tests that were positive. A repeat pregnancy test done in the clinic subsequently gave a positive result. An ultrasound scan was carried out but no intrauterine echo was detected. Blood was then taken to measure the beta human chorionic gonadotropin (β-hCG) level and this was repeated 2 days later. The β-hCG levels in both samples were raised and the patient was immediately referred for laparoscopy. At surgery, a distended right Fallopian tube was found and subsequent microscopy confirmed a right tubal ectopic pregnancy.

One week later the patient attended for follow-up. Arrangements were made, in conjunction with Organon (Implanon's manufacturer), to have blood taken for serum etonogestrel assay. This involved attendance at the local biochemistry laboratory where 10 ml blood was taken, processed and transported by courier under dry ice conditions to the Organon laboratories in The Netherlands. The patient was given condoms to use in the interim as any hormonal contraception could have affected future assays. Once the blood had been taken the patient returned for removal of the implant. This was also dispatched to Organon in The Netherlands where it was to be tested for its integrity and residual hormone content should the blood levels of etonogestrel be found to be within the expected range. The plasma level of etonogestrel was 105 pg/ml and the daily release rate and residual content were within the range expected given the length of time the implant had been in *situ*.

The woman's body mass index was 26 (height 1.68 m, weight 69 kg). She had no history of pelvic inflammatory disease. She had undergone a laparoscopy several years previously to investigate abdominal pain, however no abnormality was found. A chlamydial screen done at that time was negative. The patient's two subsequent pregnancies had been conceived easily and had resulted in normal vaginal deliveries. Previous contraception had consisted of Depo-Provera® prior to the woman's first pregnancy and the progestogen-only pill between pregnancies and immediately following her second pregnancy. Her only medication had been the selective serotonin re-uptake inhibitor, sertraline, 100 mg daily taken for an 18-month period up until approximately 2 months prior to her presentation. She had regular periods during the 2 years in which Implanon had been *in situ*.

Discussion

Implanon is a subdermal implant comprising an ethylene vinyl acetate copolymer cylinder with a core containing 68 mg etonogestrel, the biologically active metabolite of desogestrel, a progestogen widely used in oral contraceptives.[1] Clinical trials performed during the implant's development reported no pregnancies. In 1998, data were available for 4103 woman-years (in excess of 53 000 treatment cycles) giving a Pearl index of 0.0.[2] Implanon was introduced in Europe in 1998 and in the UK in October 1999. Experience of Implanon's use since then has produced some unintended pregnancies, although in many of these cases the conceptions have occurred as a result of failures arising from non-insertion, prior conception, drug interaction with enzyme inducers, and so on, rather than due to primary failure of the contraceptive effect.[3,4]

Implanon achieves its contraceptive effect by inhibition of ovulation and by effecting changes in the cervical mucus which hinders the passage of spermatozoa.[1] The release rate of etonogestrel decreases with time so that by the end of the first year of use the mean concentration of etonogestrel is 200 (range, 150–261) pg/ml and by the end of the third year is 156 (range, 111–202) pg/ml.[1] There needs to be a plasma level of etonogestrel of at least 90 pg/ml to suppress ovulation.

So why did this woman become pregnant? She was not overweight and had no history of use of enzyme-inducing drugs that could have predisposed her to ovulation. The fact that the residual content and calculated release rate of hormone were within the expected range would also tend to exclude extra rapid or slow metabolism of the hormone. Her plasma level of etonogestrel was 105 pg/ml, which is below the lower end of the range for the end of the third year of use but still higher than the level required to suppress ovulation. *In vitro* studies have shown that sertraline is a weak inhibitor of cytochrome P245, an enzyme involved in the elimination of Implanon.[5] Sertraline, while the patient was taking it, would therefore have tended to increase the plasma level of etonogestrel, albeit weakly. With Norplant®, another progestogen-only subdermal implant, there have been pregnancies reported in the final years of the implant cycle.[6] Perhaps for our patient an etonogestrel level of 105 pg/ml was insufficient to suppress ovulation, which had been prevented from occurring while she was taking sertraline by the small increase this drug produced in the plasma concentration? The product characteristics for Implanon state that no specific interaction studies have been done[1] and so could an interaction have been responsible for ovulation?

The other interesting aspect of this case is the extrauterine nature of the pregnancy. There were no predisposing factors for this, namely no previous pelvic

J Fam Plann Reprod Health Care 2007; **33**(2): 125–126
(Accepted 10 July 2006)

Family Planning Clinic, Grangemouth Health Centre, Grangemouth, UK
Patricia M N Henderson, MBChB, DFFP, *Clinical Medical Officer*
Morven D Gillespie, MBChB, MFFP, *Senior Clinical Medical Officer*

Correspondence to: Dr Patricia Henderson, Family Planning Clinic, Grangemouth Health Centre, Kersiebank Avenue, Grangemouth FK3 9EL, UK.
E-mail: p.henderson911@btinternet.com

inflammation, a negative chlamydia screen, and no abnormalities detected at the woman's previous laparoscopy. One can only postulate that once ovulation occurred, the same mechanism that is known to predispose to ectopic pregnancy with oral progestogen-only contraception was responsible in this case also. Only one certain case of an ectopic pregnancy due to genuine failure of Implanon has been recorded in the literature, and interestingly the woman in that case had also had regular periods since implant insertion.[7]

Ectopic pregnancy is a potentially life-threatening condition, and the initial reports concerning the efficacy of Implanon could lull medical staff into a false sense of security that pregnancy – let alone an ectopic pregnancy – is impossible. This case illustrates the danger inherent in this way of thinking. It also highlights the need for further study of possible interactions between Implanon and other drugs.

Acknowledgements

This case report is published with the kind permission of the patient concerned and with thanks to Iain Henderson for assistance with literature searches.

Statements on funding and competing interests

Funding None identified.

Competing interests None identified.

References

1 Implanon Implant for Subdermal Use. Organon EU SmPC RA 0450 EU S7 (REF 7.0). http://hcp.implanon.com/Images/SMPCImplanonV7_tcm624-170329.pdf [Accessed 2 July 2006].
2 Croxatto HB, Makarainen L. The pharmacodynamics and efficacy of Implanon. An overview of the data. *Contraception* 1998; 58(6 Suppl.): 91S–97S.
3 Harrison-Woolrych M, Hill R. Unintended pregnancies with the etonogestrel implant (Implanon): a case series from postmarketing experience in Australia. *Contraception* 2005; 71: 306–308.
4 Bensouda-Grimaldi L, Jonville-Bera AP, Beau-Salinas F, Llabres S, Autret-Leca E; le reseau des centres regionaux de pharmacovigilance. Insertion problems, removal problems, and contraception failures with Implanon [in French]. *Gynecol Obstet Fertil* 2005; 33: 986–990.
5 Crewe HK, Lennard MS, Tucker GT, Woods FR, Haddock RE. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 1992; 34: 262–265.
6 Sivin I, Campodonico I, Kiriwat O, Holma P, Diaz S, Wan L, *et al*. The performance of levonorgestrel rod and Norplant contraceptive implants: a 5 year randomized study. *Hum Reprod* 1998; 13: 3371–3378.
7 Mansour M, Louis-Sylvestre C, Paniel BJ. Extrauterine pregnancy with etonogestrel contraceptive implant (Implanon): first case [in French]. *J Gynecol Obstet Biol Reprod (Paris)* 2005; **34**: 608–609..

BOOK REVIEWS

Emergencies in Obstetrics and Gynaecology. S Arulkumaran (ed.). Oxford, UK: Oxford University Press, 2006. ISBN: 978-0-19-856730-1. Price: £15.95. Pages: 290 (paperback)

This book is a new addition to the Oxford Handbook Series. It is edited by a senior obstetrician and lecturer, with contributions from both senior and junior gynaecologists and obstetricians. The book deals with common obstetrics and gynaecology emergencies presenting to admission units, A&E, outpatient departments and GP surgeries.

The layout is clear and simple and the use of different colours and symbols has worked well. References are provided at the end of most chapters. A great deal of the factual knowledge is given in the form of tables but addition of more flow charts would have made it more attractive, simple and easy to remember.

The book is divided into two sections covering most important topics relating to obstetrics and gynaecology. The first section deals with obstetric emergencies, covering all topics in the antenatal, intrapartum and postpartum periods. All the chapters are well written but the chapters relating to medical emergencies in pregnancy, obstetric complications, and intrapartum procedures and complications are particularly worth mentioning.

The second section of the book deals with gynaecological conditions that are seen in emergencies and clinics. Perhaps because there are fewer emergency situations in gynaecology the authors have devoted less space to this part of the book. Nevertheless, this section covers all the important topics. Chapters on common intraoperative and postoperative complications are very well written.

Overall, this is an excellent and comprehensive yet compact book, which is easy to understand and remember. With the introduction of Modernising Medical Careers, more foundation years doctors and specialty trainees are entering the training programme with comparatively less clinical experience, and hence this book will be a source of good clinical understanding and management of obstetric and gynaecology emergencies. This book could be a pocket companion for medical students, foundation training doctors, GP trainees and midwives working in labour wards and early pregnancy clinics.

Reviewed by **Munawar Hussain**, FCPS, MRCOG
Specialist Registrar in Obstetrics and Gynaecology, Londonderry, Northern Ireland

Family Planning Masterclass: Evidence-based Answers to 1000 Questions. G Penney, S Brechin, A Glasier (eds). London, UK: RCOG Press, 2006. ISBN: 1-904752-33-0. Price: £48.00 (limited special offer price for RCOG/FFPRHC members £36.00). Pages: 594 (paperback)

Those of you who access the Faculty website are probably familiar with the searchable Clinical Effectiveness Unit (CEU) database of member enquiries. For the less Internet inclined, this text is the paper version of the responses to the first 1000 members' enquiries. The aim is to provide a "first point of reference when faced with a clinical dilemma". No personal opinions or anecdotes allowed – once evidence has been appraised for any particular question, the CEU develop an evidence-based response.

Not all responses have been updated and there is some inconsistent information. For example, we are told that follicle-stimulating hormone (FSH) is inaccurate for assessing menopause status in women on combined oral contraceptives (p. 278) and can only be useful if the woman discontinues sex steroid hormones. Fortunately, the response to the subsequent question gives more practical guidance (i.e. that FSH levels greater than 25 mIU/ml on Day 6 or 7 of the pill-free week in perimenopausal women suggests that contraception is no longer necessary). Another example is the advice on when an IUD can be inserted (p. 142). I'll stick with teaching the 2004 CEU advice[1] "up to 5 days after the earliest calculated time of ovulation in a regular cycle" rather than the cited WHO advice "within the first 12 days after the start of menstrual bleeding". The former is by far the more practical guidance.

The heavy emphasis on evidence-based medicine does leave the clinician floundering at times. We're told that there is no evidence to support an increased dose of depot medroxyprogesterone acetate (DMPA) or a reduction in the injection interval for management of abnormal bleeding in DMPA users. Couldn't the CEU at least refer to published practice which has a body of support? Many of us shorten the injection interval in women who repeatedly bleed in the couple of weeks before the 12-weekly repeat is due. Maybe no clinical evidence yet exists but there is a physiological rationale.[2]

Some advice is just plain unhelpful, such as: "where a woman refused to follow evidence-based medical advice, the practitioner would be best to refer her to a colleague". Having been on the receiving end of such advice, I'm not sure where the referring line would end!

Would I buy it? Well, it's a useful book to have to hand but pragmatic guidance would be a welcome addition and would extend the practical application of the book. A word of caution to readers is not to consider the response to your question as definitive – it is worth browsing through the book to read the different responses to similar questions.

Reviewed by **Anne MacGregor**, MFFP
Senior Clinical Medical Officer, Barts Sexual Health, St Bartholomew's Hospital, London, UK

References

1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (January 2004). The copper intrauterine device as long-term contraception. *J Fam Plann Reprod Health Care* 2004; **30**: 29–42.
2 Porter C, Rees MCP. Bleeding problems and progestogen-only contraception (FACT Review). *J Fam Plann Reprod Health Care* 2002; **28**: 178–181.