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Unintended pregnancies with the etonogestrel implant (Implanon): a case series from postmarketing experience in Australia

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Abstract

This paper describes a case series of over 200 unintended pregnancies associated with the etonogestrel implant, Implanon. These cases have been reported to the Australian Adverse Drug Reactions Advisory Committee during the first 3 years of marketing in this country. Of 218 cases included, 45 had insufficient data to assess the reason for contraceptive failure and 46 women were determined to have been already pregnant prior to Implanon insertion. Of the remaining 127 cases, the most common reason for unintended pregnancy was failure to insert the implant in 84 women. Other reasons included incorrect timing of insertion (19 cases), expulsion of Implanon (3 cases) and interaction with hepatic enzyme-inducing medicines (8 cases). The remaining 13 cases were classified as product/method failures once other reasons had been excluded. Using the 204,486 Implanon devices subsidized in this period to estimate the population exposed and the 218 pregnancies reported, the approximate failure rate in postmarketing use was 1 in 1000 insertions. These findings (and reports to medical indemnity insurers) have resulted in the development of guidelines and training for doctors inserting Implanon in Australia.

Keywords: Etonogestrel implant; Implanon; Contraceptive failure; Unintended pregnancy

1. Introduction

The contraceptive implant Implanon contains 68 mg etonogestrel which is released from a single device inserted into the upper arm [1]. Clinical trials performed during the development of Implanon reported no pregnancies; at the end of 1998, data were available for 4103 woman-years (over 53,000 treatment cycles) resulting in a Pearl Index of 0.0 (95% CI, 0.0–0.09) [2]. These trials provided sufficient evidence to support authorization of Implanon in Europe in December 1998 and subsequently in Australia.

Implanon was first marketed in Australia in May 2001 and has been subsidized under the Australian Pharmaceutical Benefits Scheme (PBS) which has allowed widespread use of this contraceptive. From the time of product launch to the end of April 2004, the Adverse Drug Reactions Advisory Committee (ADRAC) of Australia's medicines regulatory agency, the Therapeutic Goods Administration (TGA), has received over 200 reports of unintended pregnancy associated with Implanon. This paper describes these cases which have occurred during the first 3 years of postmarketing use in Australia.

2. Materials and methods

ADRAC receives reports of suspected adverse reactions to all medicines, including contraceptive devices. These spontaneous (i.e., unsolicited) reports are received from health professionals, the pharmaceutical industry and consumers. ADRAC receives around 10,000 such reports annually; all reports describing serious reactions (unintended pregnancy is classified as a serious adverse reaction to a medicine or device) are assessed by a clinician at the TGA before being reviewed by ADRAC.

All reports of unintended pregnancy associated with Implanon reported to the TGA were first assessed to determine if there was sufficient evidence of pregnancy for inclusion in this case series. Clinical evidence of pregnancy was required, for example, biochemical (serum or urinary bHCG) or ultrasonographic evidence or a pregnancy

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reported by a health professional. Each case of confirmed pregnancy associated with Implanon was then assessed to determine possible reasons for contraceptive failure. The information taken into account included the estimated date of conception from ultrasound scans or other information (to determine if the woman was already pregnant at the time of insertion), the timing of insertion (with respect to the menstrual cycle or whether postpartum insertion), any concomitant medicine use (for possible drug interactions) and evidence that the implant was actually inserted (including blood etonogestrel levels and/or location by palpation or ultrasound scanning).

Using this information, the reports were categorized into one of the following groups:

Prior conception. If the dates of conception indicated that the woman was already pregnant at the time of insertion, the report was classified as conception prior to implant insertion.

Incorrect timing. This category was assigned if Implanon was inserted outside the times recommended in the product information, that is, other than within the first 5 days of the menstrual cycle or other than days 21–28 postpartum.

Implant expulsion. This required documented evidence that the implant was seen to be expelled, for example, following wound infection at the insertion site.

Drug interaction. Etonogestrel is metabolized by the CYP 3A4 enzyme. The category was only assigned if the woman was taking a medicine likely to lower serum etonogestrel levels through induction of CYP 3A4.

Non-insertion. This term was used when there was evidence that the implant had not been inserted, for example, if the device could not be located by palpation or ultrasound scanning, or if serum etonogestrel levels were negative.

Product/method failure. This category was only used if adequate information was available on the case and all of the above mechanisms had been excluded, that is, if the Implanon was known to be still in place and there was no other explanation for contraceptive failure.

Insufficient information. If there was sufficient evidence of a confirmed pregnancy, but inadequate information to place the report in any of the above categories, the case was classified in this group.

3. Results

From May 1, 2001, to April 30, 2004 (the first 3 years following licensing in Australia), the TGA received 218 reports which had evidence of confirmed unintended pregnancy associated with Implanon. Of these pregnancies, 5 were reported to be ectopic.

The number of cases assigned to each of the categories described above is summarized in Table 1.

Of 218 confirmed reports, 45 (21%) had insufficient data provided to determine the reason for the unintended pregnancy. From gestation dates provided in the remaining reports (e.g., from ultrasound scans), it was determined that in 46 (21%) cases the woman was pregnant before Implanon was inserted.

For the remaining 127 cases, the most common reason for contraceptive failure was "non-insertion" which accounted for 84 (39%) of the reports. For some of these cases, it was documented how the Implanon had failed to be inserted, for example, it may have been found left in the introducer. In one case, the inserter had inserted a placebo implant from a training pack by mistake. For others, the reason for non-insertion was not precisely documented, but there was other evidence that the Implanon had not been inserted, for example, the device could not be found by palpation or ultrasound, and/or serum etonogestrel levels were negative.

Eight pregnancies (4% of cases) were determined to have resulted from interactions with concomitant medications. All drug interactions identified in this case series involved antiepileptic drugs, with 7 of these 8 women taking carbamazepine while using Implanon.

Thirteen women (6% cases) were assessed as having experienced product/method failure once other possible reasons for unintentional pregnancy had been excluded. In all these cases, the Implanon device was located in the correct position after diagnosis of pregnancy. Interestingly, one woman in this group was reported to have gained 10 kg in weight since insertion of the device.

Some data on usage of Implanon in Australia were also obtained. During this 3-year period, the PBS subsidized 204,486 Implanon implants and although this figure does not include free samples provided to doctors, nor any unsubsidized insertions (but may include some implants that were not inserted), it gives an estimate of the population exposed. Using this estimate and the 218 pregnancies reported (which is probably an underestimate as some unintended pregnancies may not have been reported to the TGA), the approximate failure rate for Implanon in postmarketing use is 0.1% or 1 in 1000 insertions. Because information was not available on the duration each of these implants was in situ, the women-years exposure (and hence the Pearl Index) cannot be estimated from the data presented in this paper.

Of the subsidized insertions, 86% were performed by general practitioners, 8% by obstetrics and gynecology

Table 1
Summary of the reasons determined for unintended pregnancies with the etonogestrel implant Implanon

Reasons for unintended pregnancy	Number of cases
Non-insertion	84
Incorrect timing	19
Drug interaction	8
Implanon expelled	3
Product/method failure	13
Prior conception	46
Insufficient information	45
Total cases of unintended pregnancy	218

specialists and 3% were performed by family planning doctors. The remaining 3% were performed by doctors in other specialties.

4. Discussion

The cases of unintended pregnancy described in this paper provide some useful information about "real-life" use of Implanon during the first 3 years of marketing in Australia. The clinical trials performed to support the licensing of Implanon indicated that, in terms of efficacy, it was the perfect contraceptive with a Pearl Index of 0 [2]. The early postmarketing experience reported here has identified some problems with Implanon when used outside the confines of a clinical trial.

This case series, which we believe is the largest of its kind to be published, provides useful information. Many of the cases of unintentional pregnancy were relatively easily explained, including those women who were pregnant before insertion. In clinical practice, not all women have pregnancy tests prior to contraceptive implant insertion (as in clinical trials) and thus some pregnancies from conceptions occurring prior to insertion might be expected to occur. These pregnancies are not usually classified as product/method failures, but reinforce the need to check menstrual dates and/or dates of unprotected intercourse before initiating contraception.

Eight unintended pregnancies in this series were determined to be the result of interaction of etonogestrel with hepatic enzyme-inducing antiepileptic drugs. We believe these are the first published reports of this type of contraceptive failure with Implanon. The product information for Implanon states that "no specific interaction studies have been performed with Implanon" but also states that such interactions may be expected, based on interactions reported with other contraceptives [1]. However, the product information advises the use of an additional barrier method when women are receiving hepatic enzyme-inducing drugs (and for at least 7 days after discontinuation). Implanon may not be a suitable contraceptive for women on these medicines long-term.

The most concerning findings in this case series were the pregnancies that occurred following failure to insert the implant. An earlier analysis of clinical trials suggested that the insertion procedure for Implanon was uncomplicated with a mean insertion time of 1.1 min [3]. The postmarketing experience in Australia has identified previously unrecognized complications of insertion. The reports classified as non-insertion by the TGA indicated that doctors were not aware of their failure to insert the implant at the time of the procedure. A number of adverse incident reports have also been made to medical indemnity insurers in Australia [4]. These failures highlight the need for guidelines and training for doctors inserting Implanon and the Royal Australian College of General Practitioners was enlisted to develop a consent form and checklists for both doctors and women performing the insertion. These checklists include the need for both the doctor and the patient to palpate the implant after insertion [4]. The Australian product information for Implanon now also includes very detailed insertion instructions and training courses and videos are available for doctors performing the insertion.

We believe the postmarketing experience with Implanon in Australia is instructive for both doctors and women using this device worldwide. It is also applicable to the introduction of any other new contraceptive device. Clinical trials performed before licensing of new products are usually conducted by experienced practitioners on selected populations of women. Real-life use of contraceptive products may be very different and, therefore, the importance of good postmarketing safety surveillance systems for new contraceptives cannot be understated.

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