

Implanon® consists of a core and a membrane. The core contains 68 mg etonogestrel dispersed in a matrix of ethylenevinylacetate (EVA) co-polymer and the external membrane is made of EVA co-polymer (0.06 mm).<sup>2</sup> This differs from the Norplant subdermal contraceptive device in which the levonorgestrel powder is free within the silastic cavity, and if this cavity is broken the powder will be dispersed. The specific design of Implanon® ensures a controlled release of etonogestrel over 3 years.

It is not possible to say that the prolonged heavy bleeding experienced by the patient described in this case report was due to the broken implant. In fact, 10–20% of women using Implanon® will have prolonged bleeding at some point.<sup>1</sup> In addition, there were other possible causes, including the fact that the patient had lost a lot of weight and suffered severe stress during this time. However, it remains a possibility that because of the disruption of the specially designed, controlled release mechanism, varying amounts of etonogestrel were being released which may have been responsible for the prolonged bleeding in this patient. When the implant was replaced with a new device the bleeding settled. Another concern would be that the

effectiveness of Implanon® as a contraceptive could be diminished if the rate-releasing mechanism is disrupted, although there is no evidence for this.

This case report is important in that it is the first to demonstrate that an Implanon® device can be fractured in situ. The clinical significance of this is unknown, but if a fractured device is suspected then we would recommend that it be replaced.

### Acknowledgement

This case report is printed with the kind permission of the patient concerned.

### Statements on funding and competing interests

*Funding.* None identified.

*Competing interests.* None identified.

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- 2 Guillebaud J. *Contraception: your questions answered* (3rd edn). London: Churchill Livingstone, 1999.

## Intra-vas deferens injection of styrene maleic anhydride gel for male contraception: Is it safe?

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(Accepted 16<sup>th</sup> August 2002)

*The Journal of Family Planning and Reproductive Health Care* 2002; **28**(4): 208–209

### Introduction

In developing male contraceptives, scientists have mainly focused on inhibition of spermatogenesis by hormones or the obstruction of sperm transport by an occlusive process. Ongoing male contraceptive research in India is looking at injecting the co-polymer, styrene maleic anhydride (SMA), dissolved in dimethyl sulphoxide (DMSO), into the lumen of the vas deferens.<sup>1–6</sup> The polymer obstructs or partially obstructs the transport of sperm and exhibits a spermicidal action.

Can a safe male contraceptive be developed out of the three constituent chemicals, styrene, maleic anhydride and DMSO? Styrene or styrene oxide is mutagenic, clastogenic and possibly carcinogenic.<sup>7–11</sup> In 1994 the International Agency for Research on Cancer (IARC) classified styrene oxide as probably carcinogenic to humans (Group 2A) and carcinogenic to animals.<sup>11</sup> Similarly, maleic anhydride has been reported to induce malignant tumours in rats<sup>12</sup> and is mutagenic to hamster lung cell.<sup>13</sup> The teratogenic nature of DMSO has been known to the scientific world for the last 30–40 years.<sup>14</sup> All the constituents of this male contraceptive agent are, therefore, actually or potentially injurious to humans.

Research on adult monkeys has shown that 400 mg of SMA gel is required to fully occlude the vas of male monkeys.<sup>3</sup> Lower doses of 200, 33.3 and 16.65 mg did not occlude the vas but led to dead or abnormal sperms appearing in the ejaculate.<sup>3</sup> Abnormal sperms have also

been detected in human ejaculate after the use of SMA gel to occlude the vas.<sup>1,5</sup> In the case of human subjects, a single dose of SMA co-polymer (40, 80 or 140 mg individually) can cause infertility on account of azoospermia and teratospermia.<sup>1</sup> After injection there was massive reduction of sperm counts, the sperms voided being of poor quality with low motility and viability, in addition to the sperms being abnormal.<sup>1</sup> Some parameters of sperm quality show signs of reversibility.<sup>1</sup> But contraception is still maintained for up to 10 years at least.<sup>6</sup> However, long-term infertility because of azoospermia or teratospermia might indicate the potential for future serious pathologic conditions, most notably testicular tumour or endocrine disruption, that could impair spermatogenesis and fertility if reversal is required.

### Discussion

#### Sperm death

There are two proposed mechanisms for sperm death. The first is that sperms are killed by a pH-lowering effect.<sup>1–3</sup> According to this mechanism, the co-polymer of SMA dissolved in DMSO is injected into the vas lumen and reacts with the cellular secretion, forming a stable precipitate within the lumen and making the environment inhospitable so that sperms passing through it are killed by the lowered pH. The average normal value of pH of the vas lumen in the absence of any foreign agent turns out to be 7.2.<sup>3</sup> However, after injection of SMA co-polymer the pH level reduces to 5.6.<sup>3</sup> Is sperm death actually due to the lowered pH? An

experiment with citric acid reduced the pH to the same level but it neither killed nor induced any structural abnormalities in the sperms.<sup>2</sup> Therefore sperm death may not be due to lowered pH alone.

The second mechanism proposed is known as the charge mechanism. According to this mechanism, sperms possess a negative charge and SMA has a positive charge. On interaction sperms are, therefore, inactivated and killed.<sup>2</sup> This is probably the way an alkylating agent identifies and destroys tumour cells. Therefore, the SMA co-polymer could be toxic to spermatogenic cells.

Both of these mechanisms fail to explain the sperm abnormalities seen and the suppression of spermatogenesis by the SMA co-polymer agent.

#### Effects on spermatogenesis

The SMA co-polymer affects spermatogenesis. This is clear from the fact that the sperm count declines drastically even when the luminal obstruction was almost nil or minimal. This means the production of sperm was inhibited by the co-polymer and that any sperms produced were defective. This might indicate genetic changes in the genes responsible for spermatogenesis, since spermatogenesis involves rapid cellular proliferation and is susceptible to the toxic effects of the co-polymer. If the charge mechanism is true,<sup>2</sup> the co-polymer agent could be an alkylating agent capable of inducing genetic mutations and toxicity.<sup>15</sup> The co-polymer in the range of molecular weight (MW) 90 000–120 000 may be highly toxic. As MW increases so does toxicity.<sup>16</sup> A study of cytotoxicity as a function of MW in the range 90 000–120 000 seems to be a logical precondition for establishing the mechanism of sperm interaction with the co-polymer. Unfortunately this has not been done so far.<sup>4</sup> As a result of higher MW, the co-polymer of SMA becomes non-biodegradable. It either blocks the vas lumen or changes it and causes infertility.

#### Sperm abnormalities

It has been observed that the SMA co-polymer induces a marked elevation in sperm abnormalities. The physical or chemical agent that induces sperm abnormalities might prove to be mutagenic, teratogenic and carcinogenic in nature.<sup>17</sup> An increase in the number of abnormal sperms might be the consequence of genetic damage to the spermatogenic cells. This means that the SMA co-polymer is either interfering with the integrity of DNA itself or with the expression of this genetic material.

Potentially teratogenic effects of the SMA co-polymer are equally important and could result in a defective sperm fertilising an egg.

#### Enzyme release

Sperms release the enzymes acrosin and hyaluronidase when they interact with the SMA co-polymer and, consequently, lose their fertilising ability.<sup>2,3</sup> What causes the sperm to release these enzymes? Perhaps sperms imprisoned within the more viscous co-polymer are forced to release the enzymes in an attempt to maintain an environment that will ensure survival and/or maintain nutrition. The continuous release of enzymes from the sperm is the first stage of carcinogenesis.<sup>18</sup> Cameron described an association between the release of enzymes with occurrence of cancer.<sup>18</sup> Therefore, it is assumed that an agent which is responsible for release of enzymes might be carcinogenic in nature.

Maleic anhydride has been used as a co-monomer in preparations of many polyelectrolyte carboxylic

co-polymers. Polyelectrolyte carboxylic co-polymers act as antitumour therapeutic agents.<sup>19,20</sup> The mode of activity of these polyanions appears to be through activation of microphages.<sup>20</sup> The activated microphages alter the amount of DNA in a tumour cell as well as changing the relative distribution of remaining DNA in the various phases.<sup>16,19,20</sup> Therefore, the use of an agent which interferes with DNA might initiate carcinogenesis and degrade the quality of the sperms.

#### Conclusion

Considering the nature of the constituents of SMA co-polymer dissolved in DMSO and their potential to induce sperm abnormalities and interfere with the release of enzymes, it is concluded that the safety of this method of male contraception should be called into question unless total obstruction of the vas can be guaranteed.

#### Statements on funding and competing interests

**Funding.** None identified.

**Competing interests.** None identified. The author has, however, had an opportunity to be associated with the SMA project funded by the Government of India at the All India Institute of Medical Sciences (AIIMS), New Delhi 110067, India.

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