Cancer of the colon in an egg donor: policy repercussions for donor recruitment

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This paper describes the tragic case of a young woman who died of cancer of the colon after successfully donating eggs to her younger sister. Although there is no direct link between her operation and the subsequent development of bowel carcinoma, this case imparts a feeling of unease when seen in conjunction with other cases reported during the last few years. It is a reminder that little is known of the long-term consequences of some aspects of assisted conception. Women undergoing ovarian stimulation for themselves or a matched recipient have the right to be advised, in an agreed format, that there is some concern about unproven potential risks from the stimulatory drugs. The safety of egg donors must assume priority over all other considerations, including lack of donors or any moral position. The recent decision by the Human Fertilisation and Embryology Authority (HFEA) to withdraw any form of payment or recompense to egg donors does not seem to us to be based on a balance of scientific advances, patient needs and the ethics of gamete supply. They state that the intention to withdraw payments was implicit in the 1990 Human Fertilisation and Embryology (HFE) Act. However the Act was based on the Warnock report made 6 years earlier. Even in 1990 ovum donation was uncommon and fertility drugs had not yet caused any unease. The Act provided the HFEA with discretionary powers to issue directions so that the future policies would be consistent with any emerging new medical evidence. It is imperative that the HFEA provide convincing evidence on how the current policy of payment to donors harms society, donors or recipients, and how in the UK the new policy will improve medical practice in assisted conception. Successful pilot studies must precede the implementation of any new policy. Failure to do this could cause irreversible harm to the practice of assisted conception using donor gametes, which will ultimately be against the basic aims of the 1990 HFE Act.

Key words: altruism/cancer/donor payments/egg donation/fertility drugs

Introduction
Money, morals and pragmatism are all involved in acts of gamete donation. The Human Fertilisation and Embryology Authority (HFEA) has recently announced that only those women who, without compensation, choose to undergo an egg collection procedure for the sole benefit of others will in future be acceptable as egg donors (Johnson, 1997; Sauer, 1997). This has been challenged on the grounds of being unworkable, considering the nationwide growing shortfall in the supply of eggs (Craft, 1997). There is a widespread concern at the hasty introduction of a radical policy change which is based on philosophical arguments and not medical evidence or practical considerations.

The medical risk to egg donors, the views of the profession and patients’ needs are key considerations. Eight years ago an important debate paper raised for the first time the fear that fertility drugs normally used to stimulate the ovaries of women seeking in-vitro fertilization (IVF) treatment, with resulting high levels of steroids, could be injurious to their long-term health (Fishel and Jackson, 1989). Egg donation was rare and the HFEA had yet to be formed.

The link between cancer and the old and new fertility hormones is still uncertain but in the intervening years numerous publications have heightened the profession’s unease about this possibility. Informed consent could be rendered meaningless unless patients are provided with a current and balanced account of all the medical risks, including cancer, which could be attributed to fertility drugs (Shenfield, 1996).

In egg donation, non-patient volunteers are exposed to unknown risks for the benefit of others. Family members, usually sisters, can become known egg donors and in many cultures they are preferred over anonymous donors. However, the suitability of sisters to act as egg donors has recently been questioned in a 5 year retrospective study. Sister donors showed a decreased ovarian response to stimulatory drugs, even at higher doses, and a significant increase in cancellation rates when compared with anonymous egg donors (Sung et al., 1996). In a separate study volunteer donors were also shown to have an increased prevalence of occult ovarian failure when compared with an age-matched infertile population (Morris et al., 1996). Until epidemiological studies on the safety of egg donors are available, case reports can provide the only guidance for safe recruitment. The sad case of a sister donor who developed colo-rectal carcinoma and subsequently died 5 years after ovarian stimulation is presented. Whilst accepting the limitations of a single case, we regard a publication like this as highly relevant to the future of egg donation, particularly when seen against the background of many recent reports.

Clinical details
In 1989, a 30 year old woman suffering from premature ovarian failure (POF) was referred to us, with her husband,
for IVF treatment using donor eggs. Two previous attempts at IVF elsewhere using donated eggs had not been successful. Her older sister, a 32 year old mother of two, now offered to donate. A detailed clinical history and examination confirmed that she was medically fit and fulfilled the HFEA criteria to act as a donor. The two sisters and their husbands attended for independent counselling. After examination of the reports by the ethics committee, approval for the procedure was obtained.

In May 1990, ovum donation was first attempted. The recipient was prepared for embryo transfer with incremental oestradiol valerate (Progynova®; Schering Health Care Ltd, Burgess Hill, Sussex, UK) until the endometrium matched the donor for thickness and quality on ultrasound scan. The donor’s ovaries were down-regulated using a long buserelin (Suprefact®, Hoechst Marion Roussel Ltd, Uxbridge, Middx, UK) protocol followed by follicular stimulation using daily injections of human menopausal gonadotrophin (HMG) (Pergonal®, Serono Laboratories UK Ltd, Welwyn Garden City, Herts, UK). The follicular and uterine response was monitored by serial ultrasound scans as described earlier (Ahuja et al., 1996). Considering the previous failure and the patients’ interest in embryo freezing, the treatment was discontinued at their request when only four follicles developed.

In the following cycle ovarian stimulation was repeated with increased stimulation (300 IU HMG daily). Six follicles developed which were prepared for egg collection with 10 000 IU of HCG. Thirty-six hours later six eggs were recovered. Incubation with the recipient’s husband’s spermatozoa resulted in five embryos. Three were transferred at the bipronucleate stage to the left Fallopian tube of the recipient and the remaining two embryos were cryopreserved for possible future use. The procedure was successful as a baby girl was subsequently delivered at term.

During the following 5 years there was no meaningful contact between the IVF centre and the patients.

In 1995 modified HFEA regulations required the licensed centres to send letters to the gamete providers for new instructions regarding their stored embryos. In this case after a delay the recipients advised the unit that the stored embryos should be destroyed. The unit then learnt of the family grief should be modified following cancer of the bowel.

The clinical details from the patients’ general practitioner were as follows. In May 1994, the donor sister presented with a 3 month history of an alteration in bowel habit. There was a suggestion of a slight mucoid rectal discharge. Occult blood was positive. Although clinical examination, rectal examination, proctoscopy and sigmoidscopy were all normal, colonoscopy revealed a polypoid lesion of 20 cm. At laparotomy a ‘nightmare’ carcinoma of the recto-sigmoid junction with extensive peritoneal spread to the Pouch of Douglas and elsewhere in the cavity with widespread nodal involvement was found. A segment of small bowel with its mesentery and 10 cm of ileum was resected, and a total hysterectomy and bilateral salpingo-oophorectomy were also performed. The whole tumour was apparently removed. She was given six courses of 5-fluorouracil and folinic acid. A year later she developed headaches. A metastasis eroding the base of the skull was diagnosed for which she received radical radiotherapy. She deteriorated and died soon after, with enormous ascites and hepateomegaly, just before her 39th birthday.

The other members of the family have been screened with no evidence of disease.

Discussion

There is at least one previous report describing a patient with primary ovarian cancer with metastases who presented with bowel obstruction and died 5 months after a second unsuccessful IVF treatment (Banderra et al., 1995). The rapid progression of the cancer was attributed to the mitogenic effect of fertility drugs on pre-malignant ovarian cells. Although nearly 30 000 new cases of bowel cancer occur annually in the UK, with a 30% survival after 5 years, the disease receives scant public attention (National Statistics, UK). A recent national television programme featured the limited knowledge of general practitioners and their difficulty in initiating diagnostic and treatment services (World in Action, 1996). However in this case, despite the exemplary efforts of the general practitioner, the disease was already extensive when the diagnosis was made. The general practitioner and the specialist services sustained their investigation despite a paucity of evidence until a diagnosis was made. Tragically it was too late to modify the outcome.

The aetiology of colo-rectal cancer is poorly understood and there is nothing in the literature to suggest a relationship with reproductive hormones. Similarly the link between ovulation induction and much rarer ovarian neoplasia is also not defined, but there is a growing unease about the subject, probably because of recent focused attention. There have been an increasing number of experimental, clinical and epidemiological arguments suggesting a link between ovulatory drugs and ovarian cancer but they remain inconclusive due to limitations in study design, the retrospective nature of the data and, as highlighted in a number of recent reviews, the need for more time (Rossing et al., 1994; Whittermore, 1994; Venn et al., 1995; Bristow and Kaplan, 1996a, b). However since 1989, when the possibility was first raised, a number of case reports have hinted at an association (Table I). Higher order ovarian stimulation protocols used in IVF treatments are now questioned (Edwards et al., 1996) and in a large study a relationship has recently been suggested between HMG and ovarian epithelial cancers (Shushan et al., 1996). Whether the relationship between ovarian stimulation and any form of malignancy following treatment with fertility drugs is causal or coincidental is debatable but even a tenuous link cannot be ignored.

The most immediate implications of the case reported here are threefold. Firstly, clear surveillance for all major forms of cancer is recommended for women undergoing prolonged and repeated ovarian hyperstimulation therapy. A recent large study of a cohort of 1254 women treated by IVF over a period of 12 years has indicated a significant excess risk of all site cancer in these patients (Dor et al., 1996). Similar conclusions have been drawn from a retrospective Danish study which involved nearly 2000 women over a period of 5 years (Moggaard et al., 1997).
Secondly, whilst we await confirmation that the current stimulatory drugs are not unduly harmful, we should inform patients paid or unpaid, IVF patients or matched donors, in an agreed format, of the possible link with cancer, prior to obtaining their consent for IVF treatment (Shenfield, 1996). This information must be presented in a written form which is accurate, centrally (HFEA) agreed, easily understandable and distinctly applicable to different types of patients (gravid and non gravid donors, for example). The situation is made more urgent by important advances in the pharmaceutical industry. Powerful new recombinant gonadotrophins (follitropin alpha and follitropin beta) are rapidly replacing the older urinary products (Howles, 1996; Out et al., 1996; Agrawal et al., 1997). This could compound surveillance problems for the long-term effects of these drugs.

Thirdly, reports of a link between fertility drugs and any form of malignancy have profound implications for those who generously volunteer to act as egg donors. Most egg donation is relatively recent with uncharted knowledge of the physical and psychological effects on donors and recipients alike. Published studies have concentrated on positive birth outcomes amongst childless recipients rather than on women of proven gravidity who volunteer to donate eggs to others as in the case reported here. Those who elect to take risks for others require meaningful assurance that unpleasant outcomes amongst donors have not gone unreported or been under-reported. Egg donation between sisters, as reported here, which has long been regarded as harmless, even preferable to anonymous donation, has in the light of new data begun to cause concern (Saunders and Garner, 1996; Sung et al., 1996; Lockwood, 1997). For a wife and a mother to expose herself to an increased risk of personal injury for the sake of others requires exceptionally careful consideration.

Before implementing a new policy, therefore, the HFEA, as the guardian and the only source of all verifiable data in the UK, has a duty to confirm that ovarian stimulation in volunteer egg donors does not increase the risk of cancer over and above the background rate. This will inevitably require contacting previous volunteer donors. The case reported here may not have come to light had it not been for the statutory need of the clinic to establish the wishes of the patients regarding the storage of their supernumerary embryos. Empirical findings about the actual experiences of parents and children in families created by assisted conception should form the basis of future policy, rather than uninformed opinion (Golombok, 1996).

It is worrying that financial compensation and the unsubstantiated fear of a profit motive rather than medical risks should dominate the recent debate on egg donation. The announcement from the HFEA apparently aims to achieve conformity between egg and sperm donors but it seems to assume that sperm and egg donors take equal risks; this they clearly do not. Convenient though it may be, it is similarly strange that the HFEA applied the ethos of blood donation or even sperm donation to egg donors (Johnson, 1997). They are intrinsically different and the argument of a preferred national culture cannot be used thus to encompass all areas of medicine. Contrary to the HFEA’s proposed new policy, which advocates a poster campaign to recruit volunteer egg donors, the Canadian Royal Commission on Reproductive Technologies recommended that egg donors should only be those who are themselves undergoing IVF procedures. They stated, probably on the basis of more recent evidence that was not available at the time of the Warnock Report (1984), that in the absence of any information on the long-term physical and psychological effects of the drugs and procedures, healthy women should not undergo egg donation unless they are receiving IVF or a simultaneous incidental medical procedure (National Institute of Health, 1994).

The HFEA also suggested that gamete donors who receive payments (maximum of £15 per act of donation) could be induced into giving consent (Johnson, 1997). By increasing public awareness through advertising, it is assumed that sufficient numbers of unpaid donors will be recruited. For sperm donors, this argument has been vehemently and totally rejected by the British Fertility Society (BFS, 1996), the British Andrology Society (BAS, 1997), the Royal College of Obstetricians and Gynaecologists (Cooke, 1996) and the DI network (a patient group), on the grounds that such an assumption is paternalistic as well as being a deterrent to potential sperm donors. It is supported neither by any evidence nor does it reflect the treatment needs of patients. Pilot studies involving large sums of money to recruit unpaid sperm donors have so far met with abject failure (Cooke, 1996; McLaughlin et al., 1997). We have no doubt that these arguments can be applied with greater effect to egg donor recruitment (Ahuja and Simons, 1996).

One form of egg donation which carries no extra risk of cancer is egg sharing which is now also threatened. In some countries (e.g. Israel, Denmark) egg sharing is the only form of egg donation allowed. In egg sharing, IVF patients themselves anonymously donate to matched recipients an

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**Table I.** Selected case studies indicating complications following ovarian stimulation (1992–1997)*

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of cases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian epithelial cancer</td>
<td>2</td>
<td>Nijman et al., 1992</td>
</tr>
<tr>
<td>Ovarian granulosa cell tumour</td>
<td>12</td>
<td>Willemansen et al., 1993</td>
</tr>
<tr>
<td>Ovarian cystadenoma</td>
<td>2</td>
<td>Salle et al., 1997</td>
</tr>
<tr>
<td>Ovarian metastatic strumosis</td>
<td>1</td>
<td>Balasch et al., 1993</td>
</tr>
<tr>
<td>Systemic lupus erythematosis</td>
<td>3</td>
<td>Ben-Chetrit and Ben Chetrit, 1994</td>
</tr>
<tr>
<td>Severe thrombosis</td>
<td>3</td>
<td>Aurousseau et al., 1995</td>
</tr>
<tr>
<td>Serous papillary carcinoma</td>
<td>1</td>
<td>Kamatsue et al., 1995</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>16</td>
<td>Bezzinsinski et al., 1994</td>
</tr>
<tr>
<td>Multiple melanoma</td>
<td>1</td>
<td>Kuppens et al., 1992</td>
</tr>
<tr>
<td>Adenocarcinoma of endometrium</td>
<td>3</td>
<td>Miannay et al., 1994</td>
</tr>
<tr>
<td>Endometrial stromal sarcoma</td>
<td>1</td>
<td>Waterstone and Parsons, 1992</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>1</td>
<td>Salha et al., 1997</td>
</tr>
<tr>
<td>Sertoli-leydig cell tumour</td>
<td>1</td>
<td>Chou et al., 1997</td>
</tr>
</tbody>
</table>

*Many cases have led to surgical intervention or fatality.
agreed proportion of their surplus eggs either as a gesture of goodwill or in return for subsidised treatment for themselves which is otherwise unavailable to them (Check et al., 1994; Yaron et al., 1995; Borini et al., 1996; Ahuja et al., 1996; Englert, 1996; Faber et al., 1996). No extra surgery, ovarian stimulation or risk to volunteers is involved. Neither the success rates nor the autonomy of women is compromised. A highly successful intermediate situation currently prevails in the UK whereby both volunteer egg donors and volunteer egg sharers are acceptable so long as they fulfil rigid eligibility criteria. The practice is gaining greater acceptability in the UK (Abdalla, 1996; Ahuja and Simons, 1996; Lockwood, 1997; Ridley, 1997) and women support it because they see it as a genuine opportunity simultaneously to assist themselves and someone else (Ahuja et al., 1997). Far from opposing it, it would seem logical, even desirable, that the HFEA should encourage egg sharing as a way of sustaining the supply of donated oocytes. There is no evidence of psychological or physical harm to the donors who participate in egg sharing. This was the view which predominated at a HFEA conference on gamete donation which was held at St Anne’s College, Oxford, UK on 1 June 1995. We believe it also represents the views of the majority of general practitioners, and of our patients.

Note added in proof
After this paper was submitted for publication, two important studies appeared in the literature. One complication of ovarian stimulation is the occurrence of lower limb deep vein thrombosis (DVT). According to a survey of the world literature, DVT was shown to exist with bilateral DVT (Rance et al., 1997). The proposed HFEA policy of recruiting only volunteer donors is likely to result in a low risk of ovarian stimulation or risk to volunteers is involved. Neither the success rates nor the autonomy of women is compromised. A highly successful intermediate situation currently prevails in the UK whereby both volunteer egg donors and volunteer egg sharers are acceptable so long as they fulfil rigid eligibility criteria. The practice is gaining greater acceptability in the UK (Abdalla, 1996; Ahuja and Simons, 1996; Lockwood, 1997; Ridley, 1997) and women support it because they see it as a genuine opportunity simultaneously to assist themselves and someone else (Ahuja et al., 1997). Far from opposing it, it would seem logical, even desirable, that the HFEA should encourage egg sharing as a way of sustaining the supply of donated oocytes. There is no evidence of psychological or physical harm to the donors who participate in egg sharing. This was the view which predominated at a HFEA conference on gamete donation which was held at St Anne’s College, Oxford, UK on 1 June 1995. We believe it also represents the views of the majority of general practitioners, and of our patients.

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