Fertility effects of cancer treatment

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BACKGROUND Cancer sufferers are a subfertile group, and most treatments have the potential to adversely affect gonadal function. As cancer treatment becomes more effective and survival rates improve there are more cancer survivors in the reproductive age group for whom parenting is an important consideration.

OBJECTIVE This article outlines the effects on fertility of cancer treatments and techniques to minimise the risk of infertility.

DISCUSSION The overall prospects for younger cancer sufferers to either retain their fertility or have genetic offspring is now better than ever before, due to advances in assisted reproductive technology, the appropriate use of fertility sparing surgery and other techniques to reduce the toxicity of therapy on the reproductive organs. These advances raise new moral and ethical concerns that must be considered before advising cancer sufferers of the options for preserving reproductive capacity.

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While the most immediate concern of cancer sufferers in the initial phases of treatment is survival, quality of life issues take on increasing importance as time passes from the diagnosis. One important issue is fertility. Examination of age specific cancer rates in Australia[1] indicate there were 2312 new cases diagnosed in Australia in 1998 in people less than 30 years of age, with a further 1365 new cases in patients aged 30–34 years, and 2025 new cases in the 35–39 years age group. This indicates a substantial number of people suffering from cancer for whom the preservation of fertility may well be a significant concern.

A review of paediatric cancer trials programs in the United States gives interesting insights into the increasing magnitude of the problem.[2] The review points out that while the incidence of cancer is increasing in all age groups in the US, the rate of increase is greatest in the 15–19 year age group who rate second only to those aged 65–74 years in cancer incidence. Over the past 40 years the survival rates for children with cancer have risen from 20% to over 80%, with the projected survival rate for children diagnosed with cancer in 2000 being 86%. Over that period cancer survival rates have improved throughout the American population but the improvement is much greater in children than in other age groups with a reduction in mortality of 70% for children less than five years old, 50% for those 5–14 years old and of the order of 40% for the 15–34 years age group. In 1968 the survival rate for children with acute myelogenous leukaemia was less than 10% whereas by 1993 it was over 70%. Similar dramatic improvements in survival were seen in other childhood leukaemias and paediatric solid tumours.

Furthermore, it has been pointed out that further improvements in cure rates for childhood malignancies may well depend on more selective, but probably more aggressive treatment which may well increase the risk of reproductive failure.[3]

It is therefore important that the issue of future reproductive options is considered as early as possible in the course of the management of young people with malignant disease.

Effects of drugs and radiation on gonadal function

A study of the survivors of childhood and adolescent cancer treated between 1945 and 1975 demonstrated

the fertility rate among cancer survivors to be 85% of that of a comparable, nontreated population, with males more likely to be infertile than females.[4] This is because both chemotherapy and radiation affect gonadal function.

Radiation

The effect of radiation on the gonads depends on the total dose received by the gonads in the course of treatment, and in the case of the testicles on the fractionation, which is the proportion of the total dose delivered on a daily basis. The effects of radiation on the ovaries is also dependent on the age of the patient, with younger women tolerating higher doses without loss of fertility. It must be kept in mind that it is not simply the inclusion of gonads in the radiation field that exposes them to risk, but the fact that radiation 'scatters' in normal body tissues and can therefore affect gonads excluded from the primary radiation field.

Male fertility

In general terms, testicles exposed to between 10 and 30 cGy undergo temporary oligospermia, those receiving 50-100 cGy will undergo aspermia for between 3–17 months, with full recovery usually occurring between 8–38 months. At doses of 200–300 cGy total aspermia is experienced at two months and recovery is rare.[5] Careful shielding of testicles during abdominal or pelvic radiation will dramatically reduce the risks of prolonged aspermia, which results from 'scatter' radiation within body tissues.

Female fertility

Ovaries are somewhat more resistant to radiation because, in contrast to the constant spermatogenesis occurring in the testis, cell division in the ovary is confined to a few germ cells each cycle. However, the number of oocytes decreases with age, so the ovaries of younger women are more resistant than those of older women. Doses of up to 150 cGy have little effect on younger women but will lead to ovarian failure in some women over the age of 40 years. Doses between 250 and 500 cGy will sterilise around 60% of women aged between 15 and 40, while the remainder will suffer temporary amenorrhoea. With doses greater than 800 cGy the majority of women will be permanently sterilised.[5] Given that radiation doses to the whole pelvis of the order of 50 Gy delivered in fractions of 180–200 cGy per day, five days per week are usual in the treatment of cervical cancer, it is clear that ovaries will fail early in the course of treatment. Where pelvic radiation is planned, relocation of the ovaries, with their blood supply intact, out of the pelvis can protect against ovarian failure. Internal 'scatter' can still produce ovarian failure despite this precaution. However, pelvic radiation in women may also affect the uterus directly, with one study of 10 women with premature ovarian failure following pelvic radiation having reduced uterine length, with a reduced uterine blood flow and a failure of the endometrium to respond to exogenous hormonal stimulation. These changes would obviously directly affect potential fertility whether by natural fertilisation or assisted reproductive techniques.[6]

Chemotherapy

The deleterious effects of alkylating agents such as melphalan, cyclophosphamide and chlorambucil on gonadal function was demonstrated soon after they came into general use. There is an inverse relation between the age of the patient and the dose of drug required to effect sterility.[4] Other chemotherapeutic agents are less likely to produce permanent gonadal failure, although the testicles are more likely to be affected than the ovaries.

A confounding factor in all these considerations is the effect of the disease on gonadal function. For instance, in one study, 33% of men with Hodgkin's disease had low sperm counts and impaired motility before initiation of treatment and many had evidence of impaired Leydig cell function.[7] In contrast, there is no evidence of impaired fertility in women before treatment of Hodgkin's disease.[8]

Options for preserving fertility

Preservation of fertility following cancer treatment can be achieved in a number of ways, including fertility sparing surgery, techniques of protecting gonads during radiotherapy or chemotherapy, and the preservation of gonadal tissues, ova or semen in vitro until therapy is completed.

Fertility sparing surgery

Germ cell tumours

The use of conservative surgery to preserve fertility without compromising survival is well illustrated by the management of germ cell tumours of the ovary. These extremely aggressive

tumours occur predominantly in younger women and until the advent of combination chemotherapy had a very poor prognosis overall regardless of treatment.

> 'Before the mid 1960s, virtually all patients with advanced nondysgerminomatous disease died. Even for the exquisitely radiosensitive dysgerminomas, patients who had been radiated were left with their fertility destroyed.'[9]

It was the advent of combination chemotherapy, initially using combinations such as vincristine, actinomycin D and cyclophosphamide (VAC) and then in the 1980s platinum based combinations that changed the whole picture. Germ cell tumours of the ovary are highly sensitive to chemotherapy and even advanced stage disease can be managed by removal of the affected ovary together with any obvious bulk disease, followed by chemotherapy. The opposite ovary is very rarely involved with the tumour and can be conserved, as can the uterus. While patients may experience amenorrhoea during chemotherapy, and may have an increased risk of premature menopause, fertility is generally conserved. In a review of 74 cases from Brisbane and Sydney where conservative surgery was used in the management of malignant germ cell tumours of the ovary, Low et al[9] demonstrated a survival rate of 98% for early stage disease and 94% for more advanced disease. Approximately 60% of the women were amenorrhoeic during the chemotherapy but 91% resumed normal menses on completion of the chemotherapy. There were 14 healthy live births following treatment with no birth defects. One woman proved infertile. A number of other overseas studies support these findings.[10,11]

Translocation of ovaries

Mention has already been made of translocation of the ovaries, with an intact blood supply, out of the pelvis when pelvic radiotherapy is planned. In this situation natural conception will be impossible, both because of the position of the ovaries and radiation damage to the uterus, but ova may be retrieved for assisted reproductive techniques and surrogacy thereby allowing genetic offspring to be produced.

Cervical cancer

In the management of invasive cervical cancer the standard treatment for early stage disease has been radical hysterectomy and pelvic lymph node dissection. It is now recognised that for Stage 1A1 disease, which is defined as a tumour where the depth of invasion is less than 3 mm and the breadth of the lesion less than 7 mm on a cone biopsy, the incidence of lymph node metastasis is negligible and the chance of central recurrence low, allowing conservation of fertility in younger women. It is imperative that the margins of the cone biopsy are free from any form of dysplasia or invasive disease if such an approach is to be adopted.

For patients with more advanced tumours which are still clinically confined to the cervix, without parametrial invasion (Stages 1A2 and 1B1), an experimental approach allowing conservation of fertility is the use of radical trachelectomy, where the cervix and the parametrial tissues are removed but the rest of the uterus together with the tubes and ovaries are conserved, combined with pelvic node dissection. Since the first report of the technique in 1994[12] a number of papers have demonstrated the feasibility of the approach, its apparent safety, and the possibility of normal pregnancy and delivery following the procedure. A recent British study[13] involving 30 women followed for a mean of 23 months showed no recurrences of the cancer. Of 13 women wishing to conceive eight had done so with a total of 14 pregnancies and nine live births. Six of seven premature deliveries and a single late miscarriage were most likely associated with cervical incompetence. While these and other results are encouraging this procedure must still be considered experimental until long term follow up has been achieved.

Pharmacological protection of gonadal function

In the early 1980s it was suggested that suppression of ovarian function with oral contraceptives during chemotherapy for Hodgkin's disease may assist in preserving fertility.[14] Although this technique does not appear to be effective, more recently gonadotrophin releasing hormone analogues have been shown to provide a degree of protection from follicular damage in animal models following chemotherapy.[15] A preliminary study in humans showed that only one of 62 patients treated with GnRH agonists during chemotherapy failed to resume menses after the cytotoxic was ceased, whereas 60% of a control group demonstrated ovarian failure.[16] Animal studies suggest that the use

of testosterone or gonadotrophin releasing hormone analogues may offer some protection of testicular function during chemotherapy or radiation.[17]

Collection and preservation of semen, ova, embryos or gonadal tissues

Cryopreservation of semen has been practised with considerable success for many years. Nevertheless, the volumes required for successful pregnancies following artificial insemination may not be achievable without delaying treatment. The advent of microinjection techniques makes this far less of a problem, and also helps deal with the impaired spermatogenesis seen in some men with cancer of the testis or Hodgkin's disease. Microinjection techniques, whereby a single sperm is injected into an ovum to fertilise it, offer a pregnancy rate of around 20% per cycle, which is approximately double that achieved by artificial insemination.[18]

The most widely practised technique for preservation of reproductive capacity in women undergoing sterilising cancer treatments is the creation and storage of embryos, a technique which is available in all IVF units. However, an IVF cycle takes several weeks which may not be appropriate where urgent cancer treatment is needed and involves hormonal treatment which may also be inappropriate for some cancers. For younger women and those without partners embryo storage is not applicable. There are ethical issues involved, especially relating to the fate of stored embryos if the mother dies. Finally, the chance of pregnancy following frozen embryo transfer is only approximately 10% per cycle.[18]

Other options for women include cryopreservation of oocytes, banking of follicles, culture of ovarian tissue in vitro and cryopreservation or transplantation of ovarian tissue, but none of these techniques is yet at a stage where it is practical for clinical use.[19]

In addition to the possibility of harvesting malignant cells with the germ cells or gonadal tissues, Green[3] draws attention to the risk of the transmission of germ line mutations predisposing to cancer and the possibility that the process of germ cell harvest itself might be mutagenic.

Ethical issues

New technologies develop faster than the ethical framework which may guide their use. Among the questions that need to be considered include the acceptability of offering a procedure such as ovarian cortex preservation when there is only a remote possibility of successful oocyte maturation, are the anaesthetic and operative risks involved in some procedures justifiable in the light of their extremely experimental nature, the role of parents in making decisions for children with respect to possible fertility preserving techniques which also carry risks, the ownership of preserved tissues in the case of death of the patient.[20]

Conclusion

It is important in advising patients of what is and what might be possible to preserve fertility, to seek the best available medical advice and to carefully consider the overall ramifications of information supplied.

Conflict of interest: none declared.

SUMMARY OF IMPORTANT POINTS

- Survival rates of paediatric and adolescent cancer patients are rising dramatically.
- Chemotherapy and radiotherapy have the potential to adversely affect reproductive function.
- Among the options for preserving fertility in younger cancer sufferers are fertility sparing surgery, applicable to some gynaecological cancers, pharmacological protection of gonadal function with agents such as gonadotrophin releasing hormone analogues, and the collection and preservation of sperm, germ cells or ovarian tissues.
- With the collection of ovarian tissues one must consider the possibility of the inadvertent preservation of micrometastases in such tissue.
- There are numerous important ethical issues arising from such techniques which have yet to be fully addressed.

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