Problem Solving in Cancer and Fertility

ELENI M KARAPANAGIOTOU, JULIA KOPEIKA, RUTH E BOARD, CAROLINE ARCHER, MELANIE C DAVIES, JANINE MANSI

Published in association with the Association of Cancer Physicians

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Preface

The progress made in cancer diagnosis and treatment has radically improved patient outcomes. More than 50% of people diagnosed with cancer can expect to achieve long-term survival in countries with well-developed healthcare systems. That steady and continuing improvement brings with it the requirement that we focus on the quality of life of cancer survivors. Cancer professionals and patients need to plan carefully together to manage any long-term consequences of cancer and its treatment that they may encounter. Such "Survivorship Care Plans" are widely recommended but not yet comprehensively taken up in all healthcare systems.

Increasing cancer survival rates and the trend towards a later parental age for childbirth mean that there is an increasing chance of a person being diagnosed with cancer before their family is complete. There are increasing numbers of patients for whom fertility following their cancer and its treatment has to be considered carefully; this is a central issue for these patients and professionals. The Association of Cancer Physicians (ACP) has worked with specialists in fertility on *Problem Solving in Cancer and Fertility*, bringing together the extensive and ever-increasing body of information about the way that cancer and its treatment can affect fertility, the way that fertility can be protected in many patients, and the important aspects of communication and a patient-centred approach which must underpin the provision of cancer care in this most important and sensitive area. The book will discuss exciting technological developments in the preservation and promotion of fertility in cancer patients, which has become a fast-moving field of research and innovation.

Patient concerns about their future fertility are well documented. For example, studies show that over 50% of women diagnosed with breast cancer and ovarian cancer express substantial concerns about impacts on fertility; young men diagnosed with cancer place the retention of fertility as a high priority. However, good quality discussions about fertility do not always occur between cancer patients and healthcare providers. Under some circumstances the cancer care team may prioritise the treatment on curing a cancer; some cancer professionals may lack knowledge of modern fertility preservation. There will be concerns about any risks of delay in treatment, or about increasing emotional distress if fertility is discussed in detail. However, these fertility discussions are central to high-quality survivorship for cancer patients in future. The best cancer care is delivered through a multidisciplinary team; all team members need to be aware of fertility issues for their patients, and some team members should take specific responsibilities to constantly review and audit team practice in this challenging area. The wider multidisciplinary team should involve specialists in fertility, and there need to be clear protocols to involve fertility specialists appropriately when this is needed.

This text on cancer and fertility includes a wide spectrum of issues which are illustrated as chapters and case histories. The perspective chapters cover fertility issues in women and men, including fertility preservation at the time of diagnosis; management, including drugs used during pregnancy; and survivorship issues such as conceiving after treatment, premature ovarian insufficiency, and surrogacy. There are also chapters on issues related to counselling, genetics and ethics. The case histories follow the same pathway as the chapters, but using sometimes complex histories to illustrate the principles and dilemmas.

The case histories are complementary to the chapters, and there are themes linking clinical scenarios as follows:

Female fertility and fertility preservation:
Chapters 1, 2 and Case histories 1, 2, 4, 5, 6, 21, 22

Male fertility and fertility preservation:
Chapters 3, 7 and Case histories 3, 7, 23

Cancer in pregnancy:
Chapters 4, 5 and Case histories 4, 8, 9, 10,11,

Pregnancy after cancer in women and men:
Chapters 6, 9 and Case histories 4, 9, 12, 13, 14, 15, 18, 20, 21, 22, 23

Genetic issues:
Chapter 11 and Case histories 5, 19, 22

Premature ovarian insufficiency:
Chapters 8, 10 and Case histories 14, 15, 16, 17

Counselling and ethical issues:
Chapters 9, 12, 13 and throughout many of the case histories

LGBTQ:
Case histories 22, 23

The decision by the Association of Cancer Physicians to focus a workshop and Problem Solving publication on the fertility of cancer patients is a reflection of the progress and success in cancer treatment which we all welcome. However, it also illustrates very well the challenges which we have to face to ensure the best quality of cancer survivorship and the long-term wellbeing of cancer patients.

Peter Selby, President, Association of Cancer Physicians

Eleni Karapanagiotou, Julia Kopeika, Ruth Board, Caroline Archer, Melanie Davies, Janine Mansi, Editors

David Cunningham, Chair, Association of Cancer Physicians

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Eleni Karapanagiotou, Julia Kopeika, Ruth Board, Caroline Archer, Melanie Davies, Janine Mansi, Editors

Association of Cancer Physicians

The 'Problem Solving' series of cancer-related books is developed and prepared by the Association of Cancer Physicians (ACP), often in partnership with one or more other specialist medical organizations. In this particular book, our co-editors are representatives from the Royal College of Obstetricians and Gynaecologists, and have a specialist interest in fertility.

As the representative body for medical oncologists in the UK, the ACP has a broad set of aims, including education for our own members and for non-members, including interested clinicians, healthcare professionals and the public. The Problem Solving Series is a planned sequence of publications that derive from a programme of annual scientific workshops initiated in 2014 with 'Problem Solving in Acute Oncology' followed by 'Problem Solving in Older Cancer Patients', 'Problem Solving through Precision Oncology', 'Problem Solving in Patient-Centred and Integrated Cancer Care', 'Problem Solving in Immunotherapy' and 'Problem Solving in Acute Oncology 2nd Edition'. 'Problem Solving in Cancer and Fertility' is the latest in the series.

The publication involves considerable work from members and other contributors and this work is done without remuneration, as an educational service. We have been delighted with the standard of the publications which have been well received. The BMA prize for Best Oncology Book of the Year was awarded to 'Problem Solving in Older Cancer Patients' in 2016, 'Problem

Solving in Precision Oncology' in 2017 and 'Problem Solving in Patient-Centred and Integrated Cancer Care' in 2018.

The ACP wishes to thank all the contributors to this book and our previous publications, and those which are yet to come.

David Cunningham, Chairman, Association of Cancer Physicians

Peter Selby, President, Association of Cancer Physicians

PERSPECTIVE

01 The Effects of Cancer and its Treatment on Female Fertility

Richard A. Anderson

Introduction

The treatment of cancer in young women is increasingly turning from focusing purely on survival to recognition of the long-term effects of treatment on subsequent quality of life. In this regard, fertility is a very high priority for patients. That cytotoxic therapies have adverse effects on fertility has been recognized since the very earliest days of the administration of mustard gas derivatives, and specifically in relation to the ovary, with demonstration of the effects of chemotherapeutic agents on growing follicles, resulting in amenorrhea, and in the longer term resulting in loss of fertility and premature menopause. Pregnancy after cancer is also associated with increased risk, notably of prematurity and low birth weight.[1] The recognition of the importance of late effects on fertility have been paralleled by a substantial growth in the development and provision of fertility preservation services in reproductive medicine centres and the development of the necessary close links with oncology and other services, although this remains an area where much work needs to be done in improving awareness and access to services in the UK. Fertility preservation is a complex area, requiring a balance between accurate identification of those at risk and the provision of a sufficiently encompassing service, with issues including equality of access, informed decision making regarding the experimental nature of some procedures and provision of funding. From the patient's perspective, this is all undertaken at very short notice at a time of enormous stress following a recent diagnosis when many other tests and investigations also need to be undertaken. Subsequent fertility is also part of a broader survivorship agenda, recognizing that most cancer survivors have significant health issues which may impact directly or indirectly on their fertility, for example the recognition that survivors of brain and CNS cancers have reduced chance of marriage or co-habitation. There may additionally be concerns about starting or completing a family following such a serious diagnosis, as well as concerns, now recognized to be unsubstantiated, that a pregnancy following, for example breast cancer may increase the risk of recurrence.

Recent developments

The effects of chemotherapeutic agents on the ovary will almost invariably involve loss of the growing population of follicles, related to their rapid cell proliferation and sensitivity to cytotoxic agents. This is likely to result in a rapid decline in oestrogen levels, and often amenorrhea. However it is the risk to the non-growing primordial follicle pool that is most important in determining the long-term effects, and potential recovery of the ovary,[2] as they constitute the 'ovarian reserve'. Primordial follicles are formed in fetal life and thereafter a small proportion start to grow every day; subsequently the growing follicles develop fluid-filled cavities (antra) and increasingly produce oestrogen, culminating in ovulation. The number of primordial follicles is therefore progressively depleted over time, with near-exhaustion resulting in the menopause.

Premature loss of primordial follicles, as occurs with some chemotherapies, will therefore bring forward the time of the menopause, ultimately during or shortly after treatment. Remaining primordial follicles will start to grow, thus 'repopulating' the growing follicle populations of the ovary, with restoration of menses and fertility. This may however be short-lived. Additionally, while the follicle pool is the most important target within the ovary, effects on the vasculature and ovarian stroma are also very relevant and may significantly comprise later follicle growth: these may be affected by chemotherapy as well as radiotherapy. These effects of treatment are depicted in Figure 1.1.

As the primordial follicle pool can only be determined histologically, many studies rely on surrogate biochemical or clinical outcomes. These include anti-müllerian hormone (AMH), which is produced by the smaller antral follicles (Figure 1.1), ultrasound measures of the antral follicle count and most commonly the presence or absence of menses, commonly recorded as chemotherapy related amenorrhea. AMH has become the most useful biomarker of the ovarian reserve in this and other clinical situations, particularly as it does not vary to an important degree across the menstrual cycle. It does however vary in other important clinical situations, most notably being reduced by perhaps as much as 30% in women taking the combined contraceptive pill, and may also be reduced in women with cancer at the time of diagnosis. The more important clinical outcomes are much more difficult to determine and include fertility and age at menopause, with other patient-critical outcomes such as time to pregnancy and attaining desired family size, rarely if ever described. The endocrine-related functions of the ovary, for example in supporting bone mass and quality of life through recording of issues such as hot flushes and joint pains, are also sometimes investigated and are important aspects of the non-reproductive aspects of ovarian function.

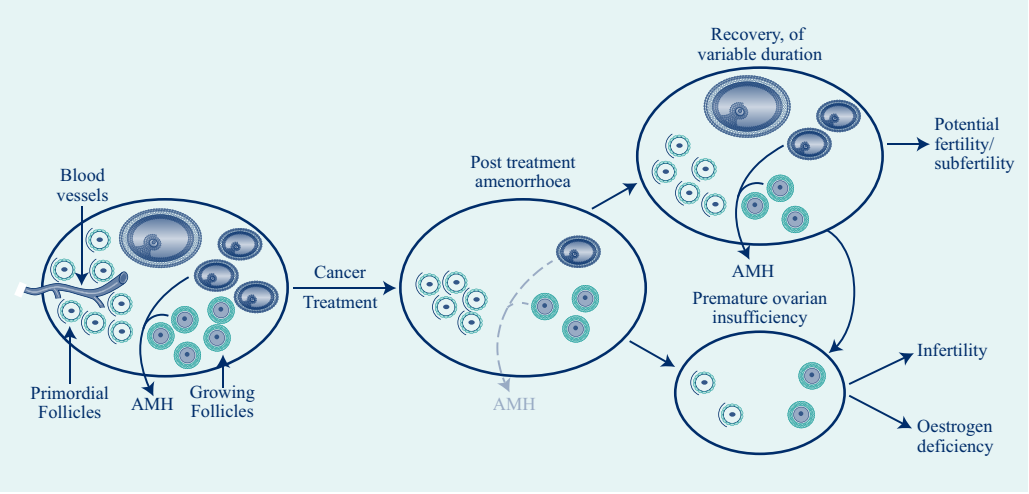

Figure 1.1 Representation of the effects of gonadotoxic treatment on the ovary. The number of primordial and early growing follicles in a healthy ovary is reduced by some chemotherapy regimens, with additional effects on the ovarian vasculature and stroma. If a sufficient population of primordial and thus early growing follicles remains, development of pre-ovulatory follicles will continue allowing the potential for post-treatment fertility. Otherwise, complete depletion results in premature ovarian insufficiency (POI), infertility and oestrogen deficiency. Ongoing post-treatment ovarian function may develop into POI, depending on the remaining ovarian reserve.[2]

In addition to the ovary, the uterus is also a key target of damage through radiotherapy to the pelvis, particular before puberty. Radiotherapy damage to the uterus may result in early or late miscarriage, premature delivery, stillbirth and post-partum haemorrhage.[3] The central control pathways of the hypothalamus and pituitary may also be damaged by surgery or cranial radiotherapy, with sometimes subtle but progressive effects on ovulatory control reported.

Due to the progressive decline in the number of follicles within the ovary with age, and the variability from one woman to the next, treatment effects are superimposed on a very wide-ranging background level of ovarian function. The effect of age is well-described, with data showing an increased prevalence of infertility with increasing age at diagnosis even in women with ongoing ovarian function, as well as changes in the prevalence of post-treatment amenorrhea. There are limited data on risk of early menopause, but for example in the case of Hodgkin's lymphoma, the varying risk with different therapies has been clearly described with minimal risk of early menopause following ABVD therapy, but with substantial and increasing risk with alkylating based therapy, pelvic radiotherapy and particularly the combination.[4] Data relating to fertility after cancer therapy are more scarce, and better provided in the paediatric than adult setting. The United States Childhood Cancer Survivors Study has provided considerable data for many years now, and recent data on women treated with chemotherapy only show the importance of specific therapies but against an overall positive finding of a hazard ratio for live birth of 0.87 (95% CI 0.81–0.92).[5] That analysis does however highlight the effect of later age at conception, with a widening of the difference between cancer survivors and their siblings in women who had not conceived before the age of 30. To broaden these data and provide an unbiased risk, we undertook an analysis of population based databases in Scotland recording all diagnoses of cancer up to the age of 40 against subsequent pregnancies, with outcomes compared to the general population standardized for age at diagnosis, interval since and deprivation.[6] Overall, this showed that women were 38% less likely to achieve a pregnancy after a cancer diagnosis than women in the general population and this was across all diagnostic groups (Figure 1.2). Cervical and breast cancer made the

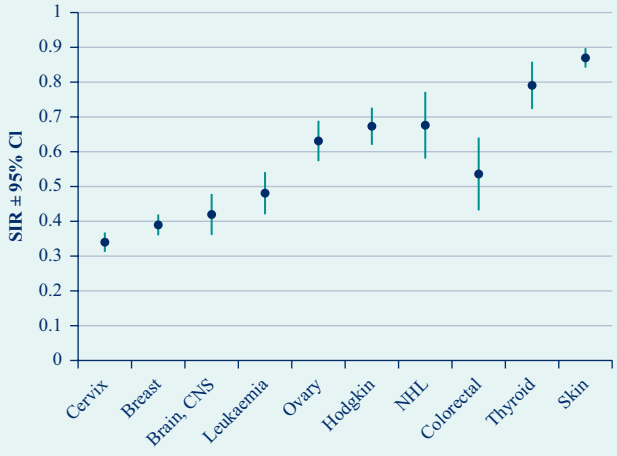

Figure 1.2 Standardized incidence rate (SIR, with 95% CI) for pregnancy after cancer by diagnosis. Data are for female patients ($n = 23{,}201$) diagnosed below the age of 40 years between 1981 and 2012 in Scotland, with subsequent pregnancies or death up until the end of 2014, compared to population controls. Standardized for age, deprivation and year of diagnosis. Data from Ref. (6).

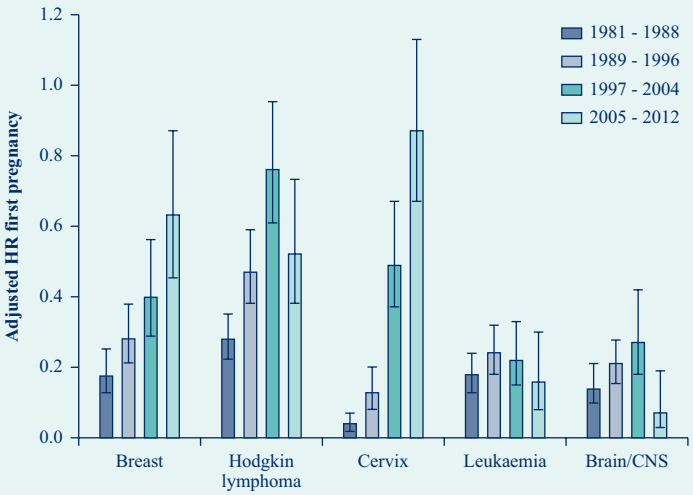

Figure 1.3 Adjusted hazard ratio (HR, with 95% CI) for first pregnancy after cancer diagnosis by period of diagnosis for women with breast, Hodgkin's lymphoma, cervical, leukaemia and brain/CNS cancers. Reprinted with permission from Ref. (6).

greatest impact with standardized incidence ratios of 0.34 and 0.39, respectively, but in both cases there have been substantial improvements in the likelihood of achieving a pregnancy across the period of analysis from 1981 to 2012, particularly for cervical cancer (Figure 1.3). This may be an effect of the introduction of cervical screening and thus earlier, less aggressive surgical treatment for cervical cancer, and changes in chemotherapy regimens for breast cancer. For other diagnoses, notably leukaemia and brain/CNS cancers, there has not been any apparent improvement in the chance of pregnancy after diagnosis over these years. Perhaps indicating greater health-awareness after cancer, this analysis also showed that the likelihood of a pregnancy resulting in termination was, in fact, significantly reduced following a cancer diagnosis, particularly in those diagnosed in childhood and adolescence. There were additional improvements in the mode of delivery, with a normalization of the rate of elective caesarean section.[1]

There has been much interest in the value of the measurement of AMH as an index of cancer treatment induced damage to the ovary, first demonstrated in survivors of childhood cancer despite their continuing to have regular menstrual cycles.[7] This finding has been replicated in many other studies and it has also been shown that pre-treatment AMH will predict long-term ovarian function, particularly in the context of breast cancer treatment.[8] In that study, all women with pre-treatment AMH <1.9 ng/ml (13.5 pmol/l) showed long-term amenorrhoea, and a value of 0.71 ng/ml (5.0 pmol/l) had peak likelihood ratio of 7 for predicting ongoing menses, with sensitivity 54% and specificity 92%. AMH very clearly distinguishes between high and low risk gonadotoxicity treatments, for example comparing ABVD treatment with BEACOPP: there is complete recovery of AMH levels in women treated with ABVD but only very low post-treatment levels following BEACOPP.[9] Intriguingly, however, even following ABVD there was evidence of an impact of age on the rate and extent of recovery, with compromised recovery in women over the age of 35.

While other articles in this series will discuss approaches to fertility preservation, it is now clear from several large randomized control trials that GnRH agonist treatment during chemotherapy for breast cancer does reduce the prevalence of premature ovarian insufficiency thereafter.[10] Meta-analysis indicates an odds ratio of 0.37, with a very similar result from an individual patient data analysis approach, with an odds ratio of 0.38. However, it is important to recognize that these studies only followed-up women for relatively short periods of time, generally no longer than 2 years, and therefore the true benefits of this apparent protective effect on either fertility or the non-reproductive endocrine aspects of ovarian function have not been clearly determined. Notably, the OPTION trial was the only large randomized controlled trial to include AMH measurement to assess ovarian reserve post-treatment, and this showed no difference in AMH levels following recovery between those who did or did not have GnRH agonist treatments during chemotherapy.[11] A wide range of other pharmacological approaches to protect the ovary are also being investigated, but these remain in the pre-clinical stage.

Conclusion

Fertility preservation is now a part of mainstream medicine, which recognizes the importance of fertility after cancer treatment to many women. There is an ongoing need for improved accuracy of patient-specific assessment of risk to their fertility and ovarian function, focusing on their proposed treatment, but also in the context of intrinsic issues, notably their age and ovarian reserve. It is to be hoped that in the future, this will allow more tailored and effective use of fertility preservation techniques, with long-term outcome studies also addressing the non-reproductive health benefits of improved ovarian function.

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