LATE REPRODUCTIVE EFFECTS OF CANCER TREATMENT IN YOUNG PEOPLE

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INTRODUCTION

Fertility preservation and pregnancy in survivors of gynaecologic cancer are becoming more important since women delay childbearing and progress in medicine has had positive impact on cancer survival[1].The improvement in surveillance and treatment of cancer in recent years result in decreased mortality among the patients. About one in 650 children below 15 years of age are diagnosed with cancer every year, with five year survival rate exceeding 75% in most cases[2]. In the USA, 72,000 adolescents and young adults defined as people aged 15-39 years were diagnosed with cancer in 2006[3]. The consequences of these are the long term outlook of treatment related morbidity and quality of life issues, not the least fertility related issues. Cancer survivors particularly the young ones face the challenges of resuming life with the same quality of life as before the diagnosis and treatment of the cancer. Evidence is abound that diagnosis of cancer in this age group interferes with their ability to complete education, develop a career, remain employed or maintain relationship[4, 5]. Indeed various organs may be irreversibly affected as a direct consequence of treatment causing other health challenges.

On the whole cancer diagnosis and treatment adversely affects the quality of life of survivors often irreversibly. Clearly this would depend on age at which cancer treatment is given on one hand, the type as well as the scope of the treatment given on the other. For instance the ovarian reserve has been shown to be impaired in dose –dependent manner among cancer survivors compared with females of similar age. Reproductive hormone levels in menstruating survivors exposed to high dose therapy are similar to those in late reproductive years[6]. For young people reproductive health issues are a specific concern especially as relates altered endocrine function and fertility and the associated psychosocial effects that comes to bear[7]. Treatment methods with clear survival benefit are often toxic to the gonads, as in the case of high dose alkylating agents and irradiation of the pelvis usually used alone or in combination with surgery. The possibility of reproductive dysfunction in young women with cancer has a recognised link with depression, post-traumatic stress and psychosocial problems. A survey among young adults with breast cancer shows correlation between reproductive concerns and depressive symptoms[8, 9, 10].

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The scope of reproductive dysfunction associated with cancer therapy varies widely depending on the treatment method or combination of methods, the type and stage of the cancer as well as the age at treatment and reproductive wishes of the patient. Both male and female reproduction can be compromised. In the case of the male the most frequently employed fertility preservation strategy is in vitro cryopreservation of sperm which is often obtained none invasively. The challenges of obtaining mature female gametes are obvious limitations for this technique in the female thereby compounding the problem further.

Gynaecologist, particularly oncologist have a duty of care in educating and sign posting young cancer patient on the reproductive effects of therapy, strategies for fertility preservation and respective measures of reproductive reserve. Evidence however points to the contrary that these patients seldom receive sufficient oncofertility counselling from their providers[11, 12]. Oncologist themselves posit that they seldom discuss fertility preservation with the patients nor refer them to reproductive medicine services. Among reasons for this approach are the focus on the treatment of the cancer as top priority and anxieties about delay to treatment, lack of training in fertility measures and preservation methods and the perception that any such discussion only increases stress to the patients. A survey of Irish Gynaecology oncologist in 2011, elicited poor awareness of the success rates of reproductive therapy, the estimated time delays to cancer treatment occasioned by fertility saving interventions among responders and identified barriers to oncofertility referral to include: time delay, poor prognosis and clinical features of the cancer[13].This review examined the common reproductive morbidities associated with cancer treatment in young female cancer patients, outline the various fertility preserving measures and the various methods of assessment of reproductive reserve.

Reproductive Morbidity Associated With Cancer Treatment

At birth the female infant has about 2 million primodial follicles in the ovary, this rapidly regress through atresia such that at puberty the count is down to about 600000. Subsequent progressive depletion with each ovulation results in menopause when the count is down to about a thousand, usually at the age 52 years[7]. Factors such as surgery, cytotoxic chemotherapy, irradiation, genetic, hereditary and immunological are known to accelerate follicular atresia. Similarly these factors may have debilitating effect on spermatogenesis in the young male. A host of these factors are associated with cancer treatment. Table I, shows the common cancers in young people and their standard mode of treatment.

Table I: Common Cancers in Young People and Their Mode of Treatment

Cancer	Standard therapy
Germ cell tumors of the ovary	Surgery and multi agent chemotherapy
Burkitt's lymphoma	Multi agent Chemotherapy
Hodkin's lymphoma	Multi agent Chemotherapy
Uterine sarcomas	Surgery
Breast cancer	Surgery, radiotherapy and chemotherapy
Retinoblastoma	Radiotherapy
Wilm's tumour	Surgery and radiotherapy

Modalities of treatment vary in their effect, chemotherapy and radiotherapy may potentially affect all systems while surgery tends to be local in its effect and as such can be modified to limit reproductive side effects depending on the stage and type of cancer. Common effects of multi-agent chemotherapy in combination with surgery or radiotherapy include: cardiac and renal impairment, abnormal pulmonary function, and secondary malignancy. Reproductive effects are impaired gonadal function, endocrine function resulting in growth and abnormal puberty, infertility, osteoporosis and psychosocial problems[14].

The impact of radiotherapy on ovarian function is variable depending on the dose, duration and frequency of exposure on one hand and the age of the patient at the time of exposure. Effect is mostly seen in dividing cells, thus as the primodial follicles in children and adolescents are in quiescent prophase I of meiosis, they are relatively resistant to irradiation than cells in mitosis in adult population. Nevertheless the LD50, defined as the dose of irradiation required to destroy 50% of immature follicles at 2GY is relatively small, follicular damage still ensues. Younger cancer patients are known to tolerate exposure to irradiation more than young adults[15,] . Alkylating agents break the DNA in all stages of the cell cycle and are particularly gonadotoxic[16]. Similarly evidence exist that exposure to radiotherapy may affect the uterine capacity to support development of the fetus in the long term with increase in adverse pregnancy outcomes like miscarriage, abnormal placentation, preterm delivery and intrauterine growth restriction[17].

Premature Menopause

Exposure to cytotoxic agents and/or irradiation is a recognised cause of acute ovarian failure[18]. Premature menopause is the occurrence of amenorrhoea, hypoestrogenism and elevated levels of gonadotropins before the age of 40 years. This is associated with early and often times unexpected loss of reproductive potential and ovarian sex hormones with attendant cardiovascular, bone and psychosexual complications.

Premature menopause may represent the end of spectrum of ovarian failure. In its occult form women present with unexplained loss of fertility with normal levels of gonadotropins in contrast to biochemical ovarian insufficiency commonly described in patients with unexplained infertility and elevated levels of follicle stimulating hormone (FSH). Both categories of these patients may maintain some measure of menstrual function. Whereas in overt ovarian failure elevated basal levels of FSH are seen in patients with oligomenorrhea or amenorrhea and loss of reproductive function. Complete depletion of primodial follicles result in irreversible infertility, amenorrhea and markedly elevated FSH (>30mmol/L). It is pertinent to note the progress in this continuum is unpredictable but can be accelerated by cancer therapy. Where the ovarian failure precedes puberty other physiological processes like growth may be affected[19].

Clinical diagnosis is heralded by primary or secondary amenorrhea, abnormal development of secondary sexual characteristics or infertility in the older woman and vasomotor symptoms of oestrogen deficiency. Endocrine studies relate to high levels of follicle stimulating and luteinising hormones and low levels of oestrogens. It is important to differentiate treatment induced premature menopause from autoimmune and genetic related causes where the clinical course

of the disorder may be intermittent[19, 20]. In the later case sexually active women not desirous of family may still require contraception if unwanted pregnancy is to be avoided. The combine oral contraceptive pills (COCP) lend themselves well for this purpose, as it provide bone protective effects as well as the psychological benefit of monthly withdrawal bleeding mimicking normal menstruation. In women who wish to avoid menstruation this can be taken back to back to obviate withdrawal bleed.Universal use of the COCP for HRT should be mindful of the different doses of steroid hormones in the two preparations and is cautioned against by some endocrinologists.

Alternatives to the COCP among post treatment patients or where unwanted pregnancy is not a concern is cyclical combine hormone replacement therapy (HRT) or continuous combine HRT in patients that seek to avoid withdrawal bleeds[7]. Indeed patients without the uterus could use the oestradiol transdermal system (Alora) also known as oestrogen patches with similar short and long term benefits. It is prudent to bear in mind the psychological impact of using HRT in young women which constantly serve as a reminder to the cancer and its consequences. The use of the mirena intrauterine system in combination with weekly oestrogen patches achieves the same effect while seeking to limit this psychological impact. Women averse to taking hormones may use tibolone which is beneficial to vasomotor symptoms and is bone protective.

Patients with premature menopause have lower levels of testosterone, but only 13% have levels below the reference ranges. Hence androgen replacement therapy is only offered in selected patient groups: those with persistent fatigue, low libido and poor well being despite adequate HRT in the absence of depression and thyroid disease. Methyl testosterone 1.25-2.5mg per day or parenteral testosterone esters 50mg every six weeks are in common use as does subcutaneous slow release preparations every six month[21].

The concept of premature menopause is quite difficult for some women to accept, necessitating continuing counselling and support. It is best managed in a multidisciplinary team, for monitoring of treatment response, bone density and psychosexual concerns. Yearly monitoring of bone density using duel energy x-ray absorptiometry (DEXA) scans, nutritional and lifestyle issues as relates to exercise, smoking and calcium supplementation. Measures of ovarian reserve should be employed to provide patients with objective fertility counselling and aid the use of fertility preserving measures.

Infertility

Spontaneous fertility ensues in the presence of intact and normally functioning neuroendocrine system, responsive follicular pool that produces fertilisable gamete and receptive uterine milieu capable of supporting implantation of the embryo and nurturing fetal growth to term. Cancer treatment,especially radiotherapy and chemotherapy adversely affects all aspects requisite to spontaneous fertility to a variable extent. Indeed some chemotherapeutic agents are directly fetotoxic necessitating the use of contraception during cancer chemotherapy in young women.

Closely related to acute ovarian failure following cancer treatment is anovulatory infertility in patients who had chemotherapy or high dose irradiation. Wallace et al reported on the radiosensitivity of the human oocyte. The LD50 for human oocyte is 2Gy, and with a radiation dose >5Gy 95% of 2000 women had

permanent amenorrhoea[22]. Similarly the impact of chemotherapy particularly non cycle specific agents like the alkylating agent cyclophosphamide is well established. Amenorrhoea rates up to 80% have been reported with radical chemotherapy, although the out look is more favourable when young patients receive adjuvant chemotherapy[23].

Of course if treatment involved a hysterectomy, adoption and surrogacy remains the only means of having a family. Various measures have been employed to preserve fertility among young women receiving high dose chemotherapy and/or radiotherapy. Fertility conserving surgery has long been in practice before the advent of oncofertility. These include surgical transposition of the ovaries out of prospective radiotherapy field to limit irradiation damage, removal, cryopreservation and subsequent transplantation of ovarian tissue and in vitro maturation of oocyte. These will be considered in detail under fertility preservation. Hormonal treatment with progestogens in early stage endometrial cancer increasingly common in young women is employed temporarily in selected patients to delay sterilising treatment for purposes of child bearing. Other more established methods are cryopreservation of embryo and oocytes.

Preservation of Female Fertility

Infertility following cancer treatment is a recognised quality of live issue in survivors and effort should be made to help young cancer patients retain their fertility[24].The field of fertility preservation strategy is ever expanding with an array of options coming into clinical practice from laboratory research. These range from the well established methods in routine clinical practice like in vitro fertilisation and freezing of embryo to developmental methods like invitro egg maturation. In this review these will be examined with emphasis to their present applicability in current oncofertility practice and the evidence base for their effectiveness where available. In general the application of this methods depend on the age of the patient, state of puberty, type of cancer, ovarian reserve prior to therapy, intensity of cancer treatment, type, duration and frequency of treatment[25].

Embryo cryopreservation is the standard method in clinical practice[26]. Embryo freezing, subsequent thawing and invitro fertilisation (IVF) is a routine procedure in fertility clinics with well established effectiveness. Patients are hyperstimulated prior to treatment, to produce oocytes which are subsequently collected, fertilised invitro or by intracytoplasmic sperm injection (ICSI) and the resulting embryo cryofrozen (slow freezing or vitrification) and stored for future use. It presupposes that the patient is in a stable relationship, or prepared to accept donor sperm from identified or anonymous donor. Potential constraint here includes ethical, legal, cultural and religious considerations. Furthermore, this is appropriate for the post-pubertal patient but its applicability in younger patients is limited by the immaturity of the gamete[25]. The effectiveness of this method and identified constraints apart, oncologist have always been weary of the time delay that these procedures take and its potential impact on patient care and outcome of treatment. The effect of the medications used on the biological behaviour of different tumors is not exhaustively enunciated and remain a source of reservation for some.

Oocyte cryopreservation presently considered experimental remain a potential option for the

patient not in a stable relationship, those whose male partners withhold consent for creating embryo, those who themselves decline the option of creating embryo or women that are in relationship yet seek to maintain reproductive independence[27]. The procedure involves hormone stimulation of the ovaries prior to treatment to produce multiple ova. These are then collected and frozen for future use. The evidence base in terms of its effectiveness for subsequent utilisation to produce embryo is less robust, its potential nonetheless make it a viable option in these category of patients. Most fertility services will require local ethical board approval to provide this method of treatment this however shouldn't be a deterrent in the context of the oncology patient. Some fertility clinics have achieved comparable pregnancy rates with frozen as fresh eggs in invitro fertilisation.

In a recent multicentre observational study in 450 couples, 2721 oocytes were wormed, of which 2304 (84.7%) survived cryopreservation and 2182 treated with ICSI. Fertilization rate was 75.2%, 48.1% of the embryos were of top quality and the delivery rate was 26.3%. In fact when this data was stratified by recursive partitioning analysis the delivery rate increased to 46.4% in cases where more than 8 oocytes were vitrified[28]. This led the authors to recommend its routine use in clinical practice.

Beside issues of consent, egg freezing is only applicable in those patients who can delay cancer treatment to allow for ovarian stimulation and egg collection (typically 2-5 weeks) and tumors in which hormones can be used. In the others as in prepubertal girls, ovarian tissue or whole ovary cryopreservation is an alternative.

Ovarian or ovarian tissue cryopreservation is an alternative for women in whom hormonal stimulation is contraindicated or cancer treatment can not be delayed owing to the stage or cancer type. Ovarian cortical strips are taken cryopreserve or in instances the whole ovary is cryopreserved. This can be subsequently transplanted back to the patient autotransplantation or in instances where the risk of transplanting cancer cells back to the patient is a concern, eggs are isolated matured in vitro and fertilised and the resulting embryo transferred in standard manner or to a surrogate mother as appropriate. There is sufficient evidence for restoration of hormonal and fertility functions with autotransplantation of cryopreserved ovarian tissue. However the evidence base for invitro follicular maturation is rather tenuous and the method is limited to research setting. Recently Oktay et al reported consecutive spontaneous viable pregnancies after heterotropic ovarian tissue transplantation[29].

Surgical methods like ovarian shielding and/or transposition to limit the effect of irradiation have been employed with varying outcome[27]. Data is rather sparse to allow for recommendation. In rare cases of genetic cancers, preimplantation genetic diagnosis has been employed in the context of these services to limit the risk of transmitting oncogenic gametes[7]. These techniques are successfully used to screen for cancer predisposing syndromes like BRCA gene for breast and ovarian cancer, von Reckulin hausen's disease and adenomatous polyposis colon the precursor of Lynch II syndrome.

The use of GnRH analogues to suppress ovulation is commonly used in oncology

practice during potentially toxic chemotherapy to protect primodial follicles containing oocytes from damage[27]. Rachia et al treated 100 women with early breast cancer with GnRH analogues for 12 months during adjuvant chemotherapy; all the patients under the age of 40 years recovered menstrual function and overall 67% return of menstruation was observed. The pregnancy rate was however low at 3%[30].

Patients intending on the use of oncofertility services for preservation of their fertility require extensive counselling. This is best offered in specialised centres. Areas of focus should include the limited success rate of ART within none cancer and in cancer population, side effect of the cancer treatment including potential effect on developing fetus and impact on the capacity of the uterus to nurture a pregnancy to term in the case of radiotherapy and surgical methods like radical trachilectomy. Rare congenital defects known to be associated with birth resulting from these technologies like Angelman syndrome and maternal hypomethylation should be covered. The assessment of ovarian reserve prior to but particularly after treatment allows for a more objective fertility prognosis counselling.

Measures of Ovarian Reserve

The functional capacity of the ovary reflected by the number and quality of oocytes is known as ovarian reserve. Wide range of tests exist all aimed at predicting the fertility potential or possibilities either prior to or after cancer treatment. Tests carried out before treatment helps to select patients eligible for fertility preserving procedures in those deemed to have diminished reserve. Post-treatment test apart from providing fertility prognosis may help in deciding the prospect of spontaneous fertility or whether fertility preserving measures when used before treatment should be used to achieve conception[31]. It is instructive that these tests share as an end point the fertility potential, whereas fecundity should ideally be measured, especially as some treatment modes compromises the ability of the uterus to nurture a pregnancy to term. Fecundity test are still to be developed.

Available tests are broadly categorised into static and dynamic tests of ovarian reserve. Static tests assess biochemical and ultrasound parameters of ovarian reserve at a given point in time. Dynamic tests assess the ovarian response to exogeneous stimulation and involve measurement of hormones before and after the stimulation. The evidence base for various test vary in clinical practice and will be examined thus.

Ovarian antral follicle count (AFC) in combination with antimullarian hormone (AMH) is the most common static tests for which evidence abound. AMH is produced by granulosa cells in developing follicles. In natural ageing AMH levels rises at around age 37 when the woman's follicular count is in the region of 25000. In regularly menstruating women AMH is the endocrine factor most predictive of transition to menopause in four years and inversely correlates with the number of antral follicles in the ovary[32]. The mean antral follicular count in regularly menstruating women with no fertility concerns is usually high. Low AFC counts are associated with high levels of AMH and diminished fertility potential. The number of antral follicles correlates best with the ovarian age. The role of AFC and AMH combined is well established in clinical practice as a measure of the number of primodial follicles independent of the patient's age and are surrogates for ovarian

age and functional reserve.

The use of AMH and AFC as a measure of ovarian reserve has been effectively integrated in oncofertility practice[33]. High correlation between AMH and AFC is reported in post-treatment patients. Levels of both of which are significantly lower than in cancer treatment exposed cohorts compared to controls. Indeed evidence exists in longitudinal studies that showed a marked decrease in AFC and AMH following cancer therapy[33]. These tests are in the core of static measures of ovarian reserve with robust evidence base. Others include ovarian volume, baseline day 1-5 FSH, oestradiol, and inhibin B; but the evidence base for these measures is quite limited except possibly for ovarian volume[34].

Dynamic tests in clinical practice are clomiphene citrate challenge test (CCCT), GnRH agonist stimulation test (GAST) and exogenous FSH ovarian reserve test (EFORT). First described in 1987 by Navot et al CCCT involves administration of 100mg of clomiphene citrate from day 5-9 of the cycle and measurement of FSH levels on days 3 and 10. Abnormally high levels of FSH, defined as levels >10U/L correlates well with poor pregnancy rates and cycle cancellation in IVF patients. A recent metanalysis of 5 studies concluded that the post test prediction of no pregnancy for CCCT at cut-off FSH >10U/L 0.81 (95% CI 0.71-0.92)[35].

GAST was described by Padilla et al 1990, it aimed at eliciting a dose response curve rather than normal or abnormal results seen with other measures. This depends on pituitary production of FSH and LH to stimulate follicular development in the ovary the measure of which indicates the follicular reserve. In EFORT recombinant FSH is used to induce follicular growth in the ovary, this method was first reported by Fanchin et al 1994; basal oestradiol and FSH are compared with post injection levels to assess the ovarian reserve. Maheshwari et al in a recent systematic review were unable to arrive at conclusion on the predictive ability of GAST or EFORT[35].

Other Reproductive Effects of Cancer Treatment

The British childhood cancer survivor survey, studied pregnancy outcomes in both male and females survivors and their partners. Overall live birth rate among female survivors was two-third of expected. Out of 4113 singleton pregnancies in the female survivors, 72.9% resulted in live birth, 14.8% miscarriage, 11.8% termination and 0.6% still birth. The incidence of low birth weight and preterm delivery among the live born babies for whom records were available were 9% and 14% respectively. The termination rate amongst survivors of heritable retinoblastoma was up to 70% and was largely premised in the fear of transmitting the RB1 gene to the off spring. All spontaneous miscarriages attributable to the treatment exposure were observed after 12 weeks[36].

Preterm labour and low birth weight were particularly observed in survivors exposed to pelvic or abdominal irradiation as opposed to those treated with brain radiotherapy. Uterine artery Doppler studies out with pregnancy demonstrated reduced blood flow in radiation exposed uterus a factor possibly accounting for low birth weight. Similarly the compliance and distensibility of the uterine myometrium is impaired by radiotherapy exposure leading to late miscarriage and preterm delivery. These adverse pregnancy outcomes are not observed in

female partners of male childhood cancer survivors.

Psychosexual Problems

Although studies on psychosocial behaviour in emerging adulthood that compare cohorts exposed to cancer therapy in childhood and adolescent with age matched cohorts are reassuring in terms of social self-concept, social competence, family relationship, friendship and romantic relationships the incidence of such activities is significantly less in treated compared to the unexposed group. Furthermore, treatment intensity and time since diagnosis are associated with impaired adjustment indices. The cohorts compared well in their intention to get married and have children[5].

Similarly there is tendency to increased rates of post traumatic stress symptoms and psychological distress in exposed adolescents and young adults. Indeed the physical effect of radiotherapy on vaginal tissue may impact sexual function and affect relationships. Similarly changes in body image, diminish sense of sexuality occasioned by premature menopause, surgically induced body changes and related altered endocrine function adversely affect libido, self image, sexual dysfunction and relationship confidence including loss of attractiveness in the affected patients.

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