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Conservative management of reproductive cancers - Multiple choice answers Vol. 55

1. a) T b) F c) F d) T e) F

Cyclophosphamide is an alkylating agent and is not cell cycle dependent. Regardless of age, this agent is gonadotoxic and associated with loss of fertility and ovarian dysfunction. With increasing age, women are more likely to experience ovarian dysfunction, especially after age 40, when compared to their younger counterparts. GnRH agonist use, though results vary, likely has protective effects in regards to ovarian function and chemotherapy. Even if women do not retain ovarian function, GnRHa has not been shown to have a detrimental effect on ovarian function. Increasing dosages of chemotherapy has been associated with ovarian dysfunction as it contributes to continued damage of the development of oocytes or stromal cells. Ovarian function is largely genetically determined and having had previous pregnancies does not in itself affect ovarian dysfunction.

2. a) T b) T c) T d) F e) F

Ovarian and oocyte preservation are both reasonable options for women interested in fertility and require the input of a reproductive specialist. In a pre-pubertal female, only ovarian cryopreservation is an option. Ovarian transposition by removing the ovaries outside of the radiation field may protect ovarian function but would require fertility assistance secondary to the detachment from the uterus and possible uterine dysfunction. Additionally, it is important to note that despite ovarian transposition, success rates vary and loss of ovarian function is still possible. GnRH agonists would not protect the ovaries from radiation therapy. Secondary to the direct exposure of radiation and the low lethal dose required to affect the ovaries, GnRH agonists would play little to no role in ovarian preservation. Tamoxifen has no protective role either.

3. a) F b) F c) F d) F e) T

Ovarian stimulation can begin at any stage of the menstrual cycle. Choice of regimen will be influenced by a patient's baseline stage of the cycle, however, delay of treatment until a patient reaches the standard early follicular phase of the cycle (as is practiced in elective IVF treatment) is not mandatory in the context of oocyte cryopreservation.

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4. a) T b) T c) T d) T e) T

POI can be caused by all mentioned conditions and can also often be unexplained.

5. a) T b) F c) T d) T e) T

Examples of genes involved in POF cases include FMR1, DIAPH2, POF1B, FOXL2, BMP15, NOBOX, FIGLA and NR5A1.

6. a) T b) T c) T d) F e) F

AMH level is a good proxy measure of ovarian reserve but may be inaccurate, for example, in the context of Combined Oral Contraceptive Pill use. Early follicular phase FSH is a marker of follicular responsiveness to earlier phases of recruitment but only offers a very crude prediction of ovarian response to stimulation. Ultrasound assessment of ovarian antral follicle count is a reasonably reliable method to estimate the number of follicles that may be available for recruitment into a cycle of ovarian stimulation, but is subject to cycle to cycle variation. A combination of all three measures over several cycles facilitates the most accurate assessment of ovarian reserve. Inhibin levels are not helpful in assessing ovarian reserve.

7. a) F b) F c) F d) T e) F

The basis of random start protocols to achieve oocyte maturity for fertility preservation/oocyte cryopreservation comes from the principle that the menstrual cycle (cyclic preparation of the dominant follicle for ovulation and the endometrium for implantation) is superimposed on a more continuous process (where waves of maturing oocytes are embarking on a much longer journey of folliculogenesis). By uncoupling treatment regimens from the boundaries of the natural menstrual cycle, fertility specialists can assist oncology patients to access fertility preservation treatments in an expeditious manner that will not compromise their oncology treatment outcome by causing treatment delay.

8. a) F b) T c) F d) T e) T

Conservative surgery in the management of early stage cervical cancer, as opposed to radical surgery, aims primarily to reduce the morbidity associated with parametrial resection. This includes fertility sparing procedures such as conization or extrafascial trachelectomy. Simple hysterectomy, which is preferred in patients with no further fertility desire, is also classified as a conservative surgical modality. Yet, radical trachelectomy, although not conservative, is a fertility sparing technique. The parametrium is a fibrous band that separates the supravaginal portion of the cervix from the bladder. It extends on to its sides and laterally between the layers of the broad ligaments, and is composed of perivascular connective tissue and nerves that surround the uterine artery and veins. In cervical cancer staging, parametrial invasion (assessed with physical examination pre-operatively) results in upstaging of the cancer from stage IIA to IIB 1. Yet, in early stage cervical cancer (IA2 to IB1) with favorable prognostic features, parametrial spread (determined post-operatively by the pathological examination of the parametrial tissue) is almost nonexistent. This is the reason why the concept of “conservative surgery of cervical cancer” supposes a total or partial resection of the uterus that does not involve the parametria. The extrafascial technique permits removal of the intact uterine fundus and cervix, leaving the parametrial soft tissues or a portion of the upper vagina. In patients with stage IA1 disease without further fertility desire, simple extrafascial hysterectomy is the standard surgical approach. However, in

patients with stage IA2 to IB1 cervical cancer, the standard treatment is radical surgery and extrafascial hysterectomy is considered as a conservative alternative to radical hysterectomy. Lymph node metastasis is an important prognostic factor for survival following treatment of cervical cancer. Thus, in order to elucidate the nodal status and the patterns of lymphatic spread of tumor, systematic pelvic lymph node dissection or lymphatic mapping with sentinel lymph node biopsy is an integral part of surgical procedures recommended to treat early-stage cervical carcinomas. Cervical conization is usually performed to confirm the diagnosis and to help in disease staging, as the specimen obtained from this procedure permits histologic assessment of both depth of stromal invasion and extent of lateral spread. In some cases, it may allow a more precise measurement of the tumor volume. Conization is also considered for therapeutic purposes, preferably in patients with smaller and localized lesions, or when the surgical specimen includes the entire lesion as evidenced by pathology. In cases of positive margins on the initial conization specimen and if the remaining portion of the cervix is still accessible, a second conization can also be performed.

9. a) F b) T c) T d) T e) F

The recurrence and survival rates of cervical cancer patients treated with conization or simple trachelectomy reported so far compare favorably to those who have undergone radical trachelectomy. However, available data are from non-randomized studies and patients treated with conservative surgery may have been selected based on more favorable prognostic factors compared to those who had radical surgery. Despite the variability of eligibility criteria and patients care across settings, cervical cancer patients treated conservatively tend to have higher rates of pregnancy than those treated with radical trachelectomy. While the method used to conceive (either natural or medically assisted) and the proportion of women who actually seek a pregnancy after treatment need to be assessed, nearly 75% of conceptions after conization or simple trachelectomy in cervical cancer survivors have resulted in the delivery of a living newborn. When comparing the outcomes of neoadjuvant chemotherapy (NACT) followed by conservative surgery for early stage cervical cancer patients with tumor size >2cm, the pregnancy rate was reported to be 30.6% vs. 27.3% among women treated with NACT followed by radical trachelectomy. The observed difference, although slight, appears to be in favor of conservative surgery. Again, available data are from non-randomized studies and patients treated with conservative surgery may have been selected based on more favorable prognostic factors compared to those who had radical surgery. Conization has shown to significantly increase the risk of premature delivery. Given the paucity of data, there is a lack of evidence with regard to simple trachelectomy. Since the proportion of women who have had conization is higher among cervical cancer survivors treated conservatively, we can conclude that the rate of premature delivery in this subset of women is higher than in the general population. Few cases of ectopic pregnancies have been reported after conization for early stage cervical cancer, as well as after radical trachelectomy. Although previous pelvic surgery is suggested to increase the risk of ectopic pregnancy, no link has been established between the occurrence of ectopic pregnancy and prior conization or trachelectomy.

10. a) T b) T c) F d) F e) T

In recent years, several groups have retrospectively reviewed large series of patients with early cervical cancers who underwent radical surgery to determine the risk of parametrial involvement. In patients with favorable prognostic factors such as small tumor size, limited depth of invasion, absence of LVSI and negative pelvic lymph nodes on frozen section, the risk of parametrial involvement was found to be less than 1%. Patients meeting these criteria appear to be candidates for non-radical surgery. In general, small primary tumor size is associated with a low-risk of parametrial involvement. The smaller the tumor size, the lower the risk of parametrial invasion. The presence of LVSI was found to be an

independent prognostic factor for cervical cancer. There seems to be a strong correlation between positive lymph nodes in patients with cervical cancer and positive LVSI in the tumor specimen. In early stage cervical cancer patients with no LVSI, the risk of parametrial involvement is reportedly low. There is no correlation between age and risk of parametrial involvement.

11. a) F b) F c) F d) F e) F

Conservative treatment of intrauterine LNG of patients diagnosed with endometrial cancer is not ready to be implemented in standard care. Currently randomised trials are ongoing and results are pending. The effectiveness of intrauterine LNG is still unclear.

12. a) T b) T c) T d) F e) F

The only studies available are on patients with low-grade endometrioid and superficially invasive endometrial cancer.

13. a) T b) T c) T d) F e) T

Ovarian tissue cryopreservation is the only available option to preserve fertility in pre-pubertal girls who are planned for gonadotoxic treatment of their disease. This technique can be performed at any time of the menstrual cycle and does not require hormonal stimulation. For these reasons, cryopreservation of ovarian tissue is useful to selected patients who cannot delay the start of their cancer treatment. An advantage of this technique over oocyte or embryo cryopreservation is that only few days are required for the procedure as tissue collection is performed by laparoscopy, which can be done shortly after cancer diagnosis, or during a laparotomy if needed for oncological surgery. If the medications used for oocyte retrieval are contra-indicated then the ovarian cortex provides a rich source of both mature and immature oocytes which can be retrieved from the tissue when it is re-grafted and ovarian stimulation is possible.

14. a) T b) T c) T d) T e) T

Identification of key medical contacts and a multidisciplinary team facilitates the steering of patients across specialties within the tight timelines necessary for FP in cancer patients. Nurses and counsellors provide support to patients with decision making and immediate as well as ongoing care. The scientists provide laboratory expertise required for the management of gametes stored for FP and work closely with the fertility specialists at the time of gamete retrieval. A strong connection between the oncology team and the fertility specialists is required to ensure a coordinated approach with the medical attention and procedures required for cancer treatment and FP.

15. a) T b) T c) F d) F e) F

In men, sperm cryopreservation is an easily accessible and widely available option in more than 95% of patients and should be encouraged as a viable and established FP option. Embryo and oocyte cryopreservation are standard options for fertility preservation. During onco-fertility discussions, patients should be aware that data on the success of these strategies as derived from the current success rates report from ART generally where these procedures are routinely applied. Testicular tissue biopsy and cryopreservation is practiced within a “research” setting and is still regarded as experimental FP. There are no pregnancies reported to date using this technology. IVM stands for *in vitro* maturation of egg cells. This technique involves picking up immature egg cells from the ovaries or from ovarian tissue,

which are then matured in the lab. The procedure only requires a short or no hormonal stimulation prior to its performance. Gonadal suppression using GnRH analogues is only an option in women.

16. a) F b) F c) T d) F e) T

Although the temperature sensitive nature of the meiotic spindle and other cellular organelles was once considered to preclude effective and safe clinical application, development of modern techniques has overcome these problems. Results from controlled studies on oocyte cryopreservation, particularly in the context of large clinical oocyte donation programmes, have demonstrated clearly that cryopreserved oocytes have similar developmental and implantation potential to fresh counterparts. Given the extent of clinical validation of mature oocyte cryopreservation, there is no other option that offers a better prospect of future conception and less prospect of future complications with respect to ownership and use. Oocyte cryopreservation has now resulted in thousands of births worldwide and follow-up studies have shown no increase in abnormalities in the offspring. Although, the application of so called "social egg freezing" is still controversial, the evidence for its likely effectiveness cannot be disputed.

17. a) F b) F c) T d) T e) F

The technology currently used for oocyte cryopreservation can achieve similar outcomes to those from embryo cryopreservation and oocyte cryopreservation offers additional advantages in terms of flexibility for future use. Grafting of cryopreserved ovarian tissue has resulted in the resumption of ovarian function and live birth in multiple clinics worldwide. The outcomes from oocytes or embryos, whether fresh or cryopreserved, are significantly reduced with advancing female age, particularly in the late 30s. In addition, the pool of primordial follicles available when cryopreserving ovarian cortex is significantly reduced in this age group. In cases such as leukaemia and ovarian cancer, it would be preferable to cryopreserve oocytes if possible given the risk of malignant cells in the tissue. The complex pathways associated with full maturation of a human oocyte from the primordial follicle stage are only now being elucidated and the development of clinical technology based on this knowledge is still in the experimental phase.

18. a) F b) F c) F d) T e) T

The demonstration of leukaemic cell proliferation following xenografting of cryopreserved ovarian tissue demonstrates that the leukaemic cells, if present, are capable of retaining their viability. The uneven distribution of leukaemic cells in ovarian tissue means that there is a high chance of failing to detect the contamination when only a histological sample is examined. While xenografting increases the sensitivity of detection, the absence of localised pockets of malignant cells cannot be confirmed unless the entire tissue is assessed. Because it is not possible to examine all the stored tissue, whether by histology, xenografting or PCR of markers, there can never be certainty with respect to absence of contaminating leukaemic cells if the tissue is to be used as a clinical autograft. As a consequence of the answers to the above questions, elimination of leukaemic cells, most likely via *in vitro* maturation of the tissue, offers the best prospect for safe use of the tissue. Research in this area is, however, still at a relatively early stage.

19. a) T b) F c) T d) T e) T

By definition the ovarian reserve consists only of primordial follicles. A primordial follicle consists of a "quiescent" oocyte in the prophase of meiosis, surrounded by a single layer of squamous or flattened

pre-granulosa cells. Although the oocyte is said to be "quiescent", it is known to be metabolically active particularly its ability to repair its DNA to maintain the integrity of the genome. Should it not have sufficient DNA repair activity, the oocyte will die by atresia. Replenishment of the ovarian reserve after birth would require the formation of new primordial follicles from oogonial stem cells. The existence of putative oogonial stem cells in the human ovary after birth has been reported but is hotly debated. The size of the ovarian reserve is decreased by (i) the activation of primordial follicles to enter the growth trajectory called folliculogenesis, or (ii), being unable to repair damage to the oocyte DNA and undergo atresia. The mechanisms involved in activating primordial follicles to enter the growth trajectory are not fully known but likely involve the geographical location of the primordial follicles in relation to other follicles, the presence (or absence) of local growth or inhibitory factors, and the size of the ovarian reserve. Both environmental (cancer therapies, toxicants) and genetic (premature ovarian failure) factors can reduce the ovarian reserve through DNA damage of oocytes in primordial follicles leading to atresia. Chemo-and radiotherapy such as used in cancer treatment can permanently damage the DNA in oocytes or primordial follicles leading to atresia and diminution of the ovarian reserve. The degree to which this occurs depends on the dose and proximity of radiation to the ovary, and to the class of drug. Alkylators are especially harmful.

20. a) T b) T c) T d) T e) F

Many studies, both *in vitro* and *in vivo*, have shown that the activation of primordial follicles and their subsequent growth through the primary and secondary stages can occur in the absence of FSH and LH. The morphological characteristics of oocyte diameter and the shape and number of granulosa cells are used to define the stages of folliculogenesis. Primordial follicles are characterised by a single layer of squamous pre-granulosa cells outside the zona pellucida surrounding a "quiescent" oocyte. Primary follicles contain a single layer of cuboidal granulosa cells, some undergoing mitosis, surrounding a growing oocyte. Transitory follicles between the primordial and primary stages are characterised by an increasing number of proliferating cuboidal granulosa cells. Following activation of a primordial follicle, the diameter of the oocyte increases up to a maximum by the secondary stage and remains that size until ovulation. More than 99% of the primordial follicles that enter the follicular growth trajectory never ovulate. This estimate is based on the following; the size of the ovarian reserve at birth is about 300,000 [range 35,000–2.5 million]; at an ovulation rate of one per month, about 400 oocytes are ovulated over the fertile period, the remainder undergo atresia at all stages of folliculogenesis. It was believed that the growth and development of the oocyte was determined by the follicular environment and that the oocyte played a passive role in folliculogenesis. Recent research has now established that the healthy oocyte promotes early follicular growth and controls lineage differentiation of the granulosa cells into cumulus cells around the oocyte and mural granulosa cells lining the basement membrane of the follicle. Atresia or cell death in growing follicles originates in the somatic granulosa cells not the oocyte. Atresia in primordial or non-growing follicles originates in the oocyte. Death of oocytes in the ovarian reserve of primordial follicles is primarily the result of damaged DNA and maintains the integrity of the genome which is essential given that primordial follicles may reside in the ovarian reserve for up to 40 years.

21. a) T b) F c) T d) F e) T

Embryo and oocyte cryopreservation have now established as sound fertility preservation techniques. Both these techniques require using IVF at time of reproduction, but are a viable option for women to preserve fertility until after disease or cancer-based therapy. This process depends on ovarian stimulation, which takes 2–3 weeks; factors such as the extent of disease and the patient's medical condition need to be considered. Excision of ovarian tissue that can then be maintained *in vitro* has not been

established as a fertility preservation tool in females. For one, mimicking the micro environment of the ovary to support the growth of follicles through different developmental stages is difficult, and has not been proven to occur over extended periods of time. This process would also increase the risk of re-introducing cancerous cells into the body at the time of re-transplantation. Cryopreservation of ovarian tissue, which can then be re-transplanted at the end of treatment is a possible method of fertility preservation. This technique can either restore ability to spontaneous pregnancies, or the ability to derive mature oocytes that can then be retrieved for IVF. Whilst it is quite invasive, this technique avoids the risk of ovarian stimulation and preserves a larger pool of follicles. Generating oocytes from pluripotent stem cells is yet to be achieved for use in humans. This has been carried out with success, albeit low efficiency in mice. Development of this process could completely change the way that fertility preservation during disease is tackled. Ovarian suppression using gonadotropin-releasing hormone agonists (GnRHa) is used during chemotherapy to preserve ovarian function. However, this technique is not widely used as its effect in protecting against chemotherapy induced ovarian insufficiency is not yet widely understood.

22. a) T b) T c) F d) F e) T

The full process of folliculogenesis from initiation to the ovulation of a mature, competent oocyte is about 300 days in humans. Currently, our understanding of oocytes from stem cells is limited to the mouse model which is significantly shorter. In order to produce oocytes from stem cells in humans that are capable of producing viable offspring, the full, lengthy process of folliculogenesis must be recapitulated *in vitro*. This includes developing a tightly regulated culture system with adequate nutrients, cytokines, growth factors and developmental-stage dependent hormones that can be sustained over long periods of time. *In vitro* culturing methods must also support the ability of the oocyte to gain competence through the growth process. Oocyte competency is a key component of follicle growth and assessing the viability of the oocyte. The supporting somatic cells of a growing follicle have a vital role in oocyte competency and thus *in vitro* culturing technologies in a manner that is both, accurate and efficient. Mice models have used embryonic gonadal cells to create reconstituted follicles. However, sourcing human embryonic gonadal cells is highly unlikely given the invasiveness and difficulty of the process, but also due to the surrounding ethical issues. *In vitro* maturation is the only step of recapitulating follicle growth *in vitro* that has been successfully carried out with human follicles. It is the steps prior to this, i.e. *in vitro* differentiation of oocytes from stem cells (iPSCs or ESCs) and *in vitro* growth of these to the secondary stage that need to be worked on. Currently, these processes are not optimised for humans. In order for oocyte development from stem cells to occur in humans, these are essential components of the process that will need to be simulated. In addition to the technicality of the process of recapitulating folliculogenesis *in vitro*, this process also needs to be optimised for efficiency. The current studies in which mouse oocytes have been generated *in vitro* have <30% efficiency in producing competent MII oocytes, and <5% efficiency for number of pups. Given the ability of humans to sustain only 1–2 pregnancies, this process would need to deliver higher efficiency in delivering the final goal, i.e. healthy viable offspring, before it can translate into human use.

23. a) F b) F c) T d) T e) F

A primordial follicle consists of a “quiescent” oocyte in the prophase of meiosis, surrounded by a single layer of squamous or flattened pre-granulosa cells. Although the oocyte is said to be “quiescent”, it is known to be metabolically active particularly its ability to repair its DNA to maintain the integrity of the genome. Should it not have sufficient DNA repair activity, the oocyte will die by atresia. The ovarian reserve in human females is formed well before birth. The process, called oogenesis, occurs in the fetal

ovary between 150 and 250 days of gestation. At birth there are on average 300,000 primordial follicles in the ovarian reserve with a very large range between 35,000 and 2.5 million.

24. a) T b) T c) T d) T e) F

Recent research has now established that the healthy oocyte promotes early follicular growth and controls lineage differentiation of the granulosa cells into cumulus cells around the oocyte and mural granulosa cells lining the basement membrane of the follicle. Through its close association with the cumulus cells and their intercellular communication with the mural granulosa cells, the oocyte influences its own development and quality, maintains its meiotic arrest until the LH surge and prepares the follicle for ovulation. This is achieved by two TGF-β related growth factors, growth differentiation factor 9 (GDF9) and bone morphogenetic factor 15 (BMP15) produced by the oocyte and likely mediated by the heterodimer of GDF9 and BMP15, called cumulin.

25. a) F b) F c) T d) F e) F

The most common indication to date is congenital absence or abnormality of the uterus. Transplantation for other reasons is, at this time rare, and confined to isolated cases.

26. a) F b) F c) F d) T e) F

The use of the external iliac vessels is due to their proximity, ease of access and calibre. Anastomosis is reasonably straightforward under these circumstances.

27. a) F b) T c) T d) T e) F

Testicular and non-testicular cancers (e.g. leukaemia, lymphoma) are both considered significant risk factors for diminished semen quality. Hodgkin's lymphoma-associated fever has been reported as a potential infertility risk factor negatively affecting semen characteristics. Testicular cancer may be associated with an alteration in the blood–testis barrier and local immune dysregulation, with the consequent production of anti-sperm antibodies. Anti-sperm antibodies can impact sperm motility in the semen and their ability to pass through the female genital secretions, the fusion of gametes and possibly the first step of embryo development. Cancer-associated emotional stress can result in alterations in various hormone-levels such as catecholamines, prolactin, corticotrophin-releasing factor (CRF) and endogenous opioids. These changes might have effects on sperm production and function. Deficiencies of vitamins, minerals and trace elements are also commonly associated with some cancers. Because they play a significant role in the maintenance of a male's reproductive capacity, their deficiencies might negatively impact spermatogenesis. Chemotherapy gonadotoxic impact is associated with the fractionation schedule of the treatment. Treatment involving multiple administrations of low-dose chemotherapy might have more detrimental effects than exposure to higher dosages delivered in fewer administrations.

28. a) F b) T c) F d) T e) F

Fertility preservation in pre-pubertal boys presents a great challenge as mature sperm does not exist. This eliminates the possibility of sperm banking. Pubertal boys with a testicular volume of 10–12 mL should be encouraged to produce a sample. Boys at the onset of puberty may have small numbers of sperm cryopreserved after testicular biopsy or aspiration under anesthesia. Intracytoplasmic sperm injection may then result in their ability to father a child. Pre-pubertal fertility preservation is based on

immature testicular tissue cryopreservation as cell suspensions or whole testicular tissue for future fertility restoration using autografting, xenografting or in-vitro spermatogenesis. To date, resumption of spermatogenesis from grafted immature testicular tissue has been achieved in animals but not in humans. Testicular tissue cryopreservation should be recommended in pre-pubertal boys even though fertility restoration strategies based on future grafting are experimental and have not yet been successfully tested in humans. While the potential risks and benefits are not totally known, unless the procedure is offered, the opportunity to evaluate it and assess its clinical benefit will be missed. Efforts to preserve fertility in pre-pubertal children using experimental methods should be attempted under institutional review board-approved protocols.

29. a) F b) F c) F d) F e) T

Current research comparing perinatal outcomes of surrogate pregnancies compared with pregnancies after autologous IVF looks favorable. A review of outcomes of singleton live births using the techniques of autologous fresh IVF and intracytoplasmic sperm injection, autologous frozen embryo transfers, and surrogacy showed that there was no difference in the risk of pre-term birth or lower birth rate between the groups, and that birth weight was significantly higher in the gestational surrogacy group.

30. a) T b) T c) T d) T e) T

In the USA, guidelines on single or multiple embryo transfer were only followed in fewer than 42% of cases and even in Canada where it is illegal to pay a surrogate, the commercial drive to assist childless couples was such that guideline adherence was only 48%. Currently it seems ironic that the ethical stance taken by prosperous democratic countries, which has led to legislation denying, or severely restricting commercial surrogacy, leads to women travelling overseas and finding commercial surrogates from underprivileged communities. Women surveyed in the UK would prefer uterine transplantation to surrogacy, as overwhelmingly would the women of Japan.