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ONCOFERTILITY
COMMUNICATIONS

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Fertility Preservation : An Overview

Dr M Gouri Devi
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Chemotherapy and radiotherapy often result in reduced fertility in cancer patients. With increasing survival rates, fertility is an important quality-of-life concern for many young cancer patients. Around 75% of young cancer survivors are interested in parenthood.

The number of patients who access fertility preservation techniques prior to treatment are significantly low. Despite existing guidelines, healthcare professionals do not address fertility preservation issues adequately. There is a critical need for improvement in clinical care to ensure that the patients are well informed about infertility risks and fertility preservation options and to support them in their reproductive decision-making prior to cancer treatment.

Prof (Dr) Pankaj Talwar
Secretary General - IFS

When the patient is fighting cancer, the main concern for them is cure of the disease. However, with the increasing number of long term survivors we are obliged to discuss with them, before treatment, the possibility of them losing their fertility after cancer therapies.

Decade back the options and knowledge to treat them were limited but now due to the advent of reproductive medicine we have more treatment modalitiesto treat them. Five year survival rate is increasing and so is the intense desire of these loving children and young adult to have independence from iatrogenic infertility.

It has been endeavor of all of us to counsel, educate the masses about the nuances of fertility preservation and the outcome of the procedures. Many of them are experimental and have not an efficient outcome. Indian Fertility Society and Astra Zenac is initiating this bulletin to educate you all to do something for these unfortunate fighters and survivors and ease their pain and anxiety.

Fertility Preservation : An Overview

Dr Puneet Rana Arora
Guest Editor

I have been contributing in the field of Oncofertility both in UK and in India. Its now my privilege to initiate and start with series of bulletin named as 'ONCOFERTILITY COMMUNICATIONS "on behalf of IFS-SIG-Oncofertility.

Oncofertility is term used to bridge the specialties of Oncology and reproductive medicine.

The National Cancer Registry of India suggests that the annual number of patients who develop cancer in India is set to rise from about 9.79 lakhs in 2010 to 11.4 lakhs in 2020.More than 140,000 cancer patients are diagnosed in their reproductive years that is, up to age of 45 years and childhood cancer too seems to be increasing. It is believed that in 2010, every 250th adult will be a survivor of childhood cancer.Approximately, 40-80% of females face possible infertility as a result of their cancer treatments that is, chemotherapy, radiation, and surgery.

Improvement in cancer management and increasing survival rates has created a need for oncofertility. Unfortunately, fertility preservation services are rarely offered or even discussed with the patient before starting cancer therapy. Hence it is very important to raise awareness not only among patients but also among physicians treating cancer in such patients.

Empathy and Sympathy is the key to any medical specialty and is an important aspect of reproductive medicine but is an absolute necessity for Oncofertility. An individual is undergoing and understanding an important quality of life issue by preserving fertility at the time when they are diagnosed with life threatening disease.

I hope to provide insight and understanding of this sub-specialized field in a manner, which will help our fraternity to approach such patient in an evidence-based manner.

Dr Jayesh Amin
SIG Chair - ONCOFERTILITY

Fertility preservation is an innovative technique which requires multi disciplinary approach. Our colleagues in the field of oncology as well as general public need more awareness about the subject and therefore lot of scope for training is the requirement.

UPCOMING TOPICS

1.	International and National Review of uptake of Oncofertility	February-*2019*
2.	Ethical, Logistic and Legal aspects of Fertility Preservation	April-*2019*
3.	Breast diseases and Fertility Preservation	June-*2019*
4.	Fertility preservation in Males	August-*2019*
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Fertility Preservation: An Overview

i. INTRODUCTION

Over the last decades, advances in oncologic treatment has led to an improvement in the long-term survivors, due to a decrease in mortality. This improvement is often gained through the use of more aggressive chemotherapeutic substances. Cancer treatment, especially with alkylating agents or ionizing radiation can lead to loss of follicular poolin the ovary leading to premature ovarian failure which could lead to infertility.

With increase in number of long-term cancer survivors, fertility has become an increasingly important quality of life issue, as 4–5% of newly diagnosed cancer patients are younger than 35 years old. There are now enough studies to document that if the risks of infertility are not discussed properly before cancer treatment, cancer survivors may experience prolonged anger and grief when they are unable to conceive. Numerous oncology societies now recommend that health care providers should discuss fertility with their patients as a part of their counseling before cancer therapy, and should be prepared to refer to fertility units for discussion related to preserving fertility prior to initiating cancer treatment. Currently, several options are available for fertility preservation in young cancer patients; however, the only established option for male patients is sperm cryopreservation. For women both embryo cryopreservation and oocyte cryopreservation are considered as well established methods, ovarian tissue cryopreservation at the moment is offered in research setting but do predict a promising additional method for fertility preservation for future. Ovarian tissue cryopreservation is a good alternative option for women who cannot delay cancer treatment or with hormone dependent tumor. It is the only option for pre-pubertal girls who want to preserve fertility before cancer treatment.

While fertility preservation is recognized as an important issue, work still needs to be done to educate patients and those taking care of these patients about the issues and options for fertility preservation.

The main barriers of fertility preservation include lack of knowledge on fertility preservation, attitude and behaviors of health care providers, and time constraint before cancer treatment. In spite of many barriers, a new global trend for fertility preservation is encouraging. Fertility preservation strategies were initially developed and applied in Western Europe and North America, but those applications are no longer limited to certain geographic areas or socio-economic classes. When considering that fertility preservation is one of the most important quality of life issues in young cancer survivors worldwide, it is imperative to promote and educate to every individual undergoing cancer treatment.

ii. EFFECT OF CHEMOTHERAPY AND RADIOTHERAPY ON GAMETES

Oncofertility is an interdisciplinary medical field at the intersection of oncology and reproductive medicine that expands fertility options for cancer survivors. Oncofertility bridges the specialties of oncology and reproductive endocrinology with the purpose of maximizing the reproductive potential of cancer patients and survivors.

Cancer treatments, including chemotherapy, radiation, and surgery, may impair or destroy a person's ability to have children later in life. For women, these therapies can cause ovarian damage that can lead to genetically damaged oocytes, ovarian failure, early menopause, or other reproductive problems. For men, treatments can similarly cause damage to the testes that interfere with sperm production and testosterone secretion.

The extent of the follicle loss depends on the type of cytotoxic treatment, the substances and dosages used and also importantly age of the patient. Treatment-induced infertility is a major issue for long-time survivors of cancer, especially as many young cancer patients might not have completed their family at the time of diagnosis and treatment.

Due to the development of new techniques for fertility preservation and improvements in the efficacy of those treatments, fertility preservation methods are available and can be implemented in the oncologic treatment. However, to counsel patients, the effect of cytotoxic treatment on the ovarian reserve has to well be understood.

Most of the chemotherapeutic agents can be classified according to the phase of the cell cycle, in which they are active. Additional, some, like alkylating agents, are cell-cycle-nonspecific. The action site of each chemotherapeutic agent is different. Alkylating agents act on the DNA, antimetabolites on DNA synthesis and spindle poisons on the process of mitosis. Therefore, the use of a specific agent will define the aspects of ovarian function, which are likely to be more sensitive regarding this substance.

Chemotherapeutics are designed to act on dividing cells, so, concerning the developing oocyte, there will be different vulnerabilities. The oocytes are in a meiotic arrest and non-dividing, although rapidly growing in the developing follicles. The granulosa cells of the follicle will proliferate during follicle maturation. Growth of the oocyte and of the granulosa cells are linked closely to each other. Therefore, damage of the granulosa cells will lead to damage of the oocyte. Doxorubicin, an anthracycline, and Cyclophosphamide, which belongs to the group of alkylating agents, both seem to affect mainly the granulosa cells, whereas Cisplatin preferably targets the oocyte itself. There is substantial evidence, that alkylating agents, e.g. Cyclophosphamide, are highly ovotoxic. The effect on the ovarian reserve is dosage-dependent and another key-factor for the risk of POF is the age of the patient.

Besides the above mentioned effect of the chemotherapy on the follicle pool, chemotherapy leads also to injuries of the blood vessels. Blood supply to the ovaries is an end artery system. Therefore,

narrowing and/or obstruction of blood vessels will lead to a reduction and/or a shut-down of blood supply to the dependent areas. Local ischemia will result in the local destruction of normal ovarian cortex with loss of primordial follicles.

This process will lead subsequently to focal fibrosis of the ovarian cortex of mature females. Histopathologic examinations of the ovaries, exposed to chemotherapy, showed a number of triangular fibrotic areas without primordial follicles and replaced by normal ovarian cortex. The pattern of the ovarian injury is not related to any specific chemotherapy agent and neither it is age dependent. The same anatomic alterations in the ovarian blood vessels have been found also in young girls after chemotherapy.

Another explanation for this observation could be the link between follicle growth and angiogenesis. It seems, that angiogenesis occurs in the theca layer of follicles in the early process of follicular growth and, that increased vascularity or development of capillary network is closely associated with the active cellular proliferation and steroid production occurring in the early stages of folliculogenesis. If cytotoxic treatment leads primarily to the destruction of the preantral follicles, no cellular proliferation and steroid production will take place, and subsequently the impulse for angiogenesis and vascular growth is lacking.

Most probably, the deleterious effect of chemotherapy on the ovarian follicle pool is a combination of damage to the ovarian vessels, and direct effect of the chemotherapeutic agents on the primordial follicles. Whereas, the first mentioned mechanism will lead to segmental loss of primordial follicles, the second will induce equally distributed disappearance of the follicles throughout the ovarian cortex.

Assessment of chemotherapy-induced ovarian follicular depletion

The parameters, reflecting best the ovarian reserve, are the Anti-Muellerian-Hormone (AMH) and the ultrasonographic Antral-follicle-count (AFC). AMH is mainly produced in primary, preantral and small antral follicles. The physiologic task of AMH is, to inhibit recruitment of primordial follicles into the pool of growing follicles. In mice, the absence of AMH resulted in an increased rate of recruitment of primordial follicles and earlier exhaustion of the primordial follicle pool.

AMH is stable through the menstrual cycle, and not influenced by any hormonal treatment given. Therefore, it can be used as a marker of follicular depletion after chemotherapy. 1 week after chemotherapy, a sharp and significant decline of the AMH-level can be seen as a result of chemotherapy-induced damage to the growing follicle. In the second / third week after chemotherapy, AMH-levels started to increase, suggesting an acute effect followed by a recovery period. This pattern is independent from the type of chemotherapy used. The reduced/absent level of AMH will lead to an increased recruitment of follicles, and the growing follicle will be vulnerable to the next cycle of chemotherapy. Subsequently, this process will lead to a more rapid decline in the primordial follicle pool, caused by chemotherapy cycles, given at intervals.

AMH can be used to evaluate the effect of the chemotherapy on the ovarian reserve. Additional, the pre-treatment level of AMH could be a predictor for the patient's risk to develop POF after chemotherapeutic treatment.

Radiotherapy

The granulosacells seem to be the cells of the follicle, which are more sensitive to radiation, compared to the oocyte. Within a few hours of radiation, pyknosis can be seen in the granulosa cells. Pyknosis is the process of irreversible condensation of chromatin in the nucleus of a cell, undergoing necrosis or apoptosis. This can be observed even before any changes in the oocytes are detectable. Due to the loss of the granulosa cells, the oocyte will lose viability and the follicle will getatrophic.

Radiotherapy is well recognized to cause destruction to the ovarian pool. However, it is difficult to predict the extent of the damage. In 1989, the dose of radiation, required to destroy 50% of primordial follicles, so called LD50-dose, to be < 4 Gy has been estimated. In 2003, after applying the Faddy-Gosden mathematical model of ovarian follicle decay, the LD50 was revised to be < 2Gy. Additional, as for the risk of premature ovarian failure after chemotherapy, the existing ovarian reserve and, therefore, the age of the patient, is important. With advancing age, the ovarian reserve will decline, so, obviously, the effective sterilizing dose (ESD) will decrease with increasing age. The ESD refers to the dose of fractionated radiotherapy [Gy], at which premature ovarian failure occurs immediately after treatment in 97.5% of patients. ESD at birth is 20.3 Gy, at 10 years 18.4 Gy, at 20 years 16.5 Gy, and at 30 years 14.3 Gy . The mean sterilizing dose is the dose that will induce immediate ovarian failure in 50% of women. The combination of the knowledge of the oocyte radiosensitivity with the computed tomography (CT) radiotherapy, which provides a reliable three-dimensional determination of the ovarian radiation dosages applied, allows the calculation of the surviving fraction of oocytes and therefore the assumed age of menopause.

Besides the effect of the radiotherapy on the ovarian reserve, additional the effect of radiotherapy on the uterus and on the lining has to be considered. A successful pregnancy will require not only a viable embryo, but also a uterine cavity that is receptive to embryo implantation, and a uterus that has the ability to accommodate normal growth of the fetus to term. Radiation of the pelvis, especially when the uterus is in the radiation field, is associated with a smaller uterine volume. The smaller volume can be the result, either of direct radiation to the uterus itself, and/or of the reduced hormonal levels, associated with impairment of ovarian function or premature ovarian failure. Irradiation affecting the uterus in childhood and adolescence is associated with a raised incidence of spontaneous miscarriage and intrauterine growth retardation secondary to reduced elasticity of the uterine musculature and uterine vascular damage.

In males, degree of impairment after radiotherapy depends on the radiation dose, radiation field, fractionation schedule, and age at the time of treatment. Radiation doses as low as 0•1–1•2 Gy can impair spermatogenesis, with doses of more than 4 Gy causing permanent damage.

Apart from radio and chemotherapy the disease itself could affect fertility by causing gonadal dysfunction. In the males Hodgkin's disease, soft tissue sarcoma (stage IV) and metastatic Ewing's sarcoma have impaired semen quality even when assessed before treatment.

Besides malignant condition, loss of fertility is also observed in non-malignant conditions where cytotoxic drugs are used i.e. systemic lupus erythematosis and other rheumatological diseases.

iii. ISSUES TO BE ADDRESSED PRIOR TO RECOMMENDING FERTILITY PRESERVATION

When deciding to offer fertility preservation to people diagnosed with cancer, risk assessment is very essential. One needs to take into account diagnosis, type of cancer, age of the patient, treatment plan and expected effect on fertility after cancer treatment.

Although the prediction of fertility after treatment is very difficult one needs to assess potential markers of gonadal damage. These markers are establisted in patients who have attained puberty, but their role in pre-pubertal individiuls is still not very reliable although certain markers are emerging. While strategies exist for fertility preservation in sexually mature patients, very few treatments benefit younger patients who are at risk of infertility after treatment. However, several newer therapeutic interventions are avaliable today, though scientific, technical, legal, and ethical issues need to be addressed.

It has been seen that the treating oncologist does not give full information of need and options of fertility preservation to the cancer patients. In a study conducted by Schover et al 2002a., showed that as many as 91% of health professionals felt that sperm banking should be offered to all patients at risk, but 48% of them state that they either never bring up the topic or do so in, 25% of instances. This and other surveys (Crawshaw et al., 2004, Zapzalka et al.,1999) on professionals revealed important knowledge deficiencies with regards to advanced fertility preservation techniques especially in pre-pubertal individuals also. A qualitative study on oncologists of adult patients also revealed lack of knowledge on fertility preservation resources as a major barrier to discussion (Quinn et al., 2007a). There is also limited interaction of the oncologist with the fertility specialist and 64.3% of the oncologist reported difficulties with regard to access to centers providing fertility preservation. In many cases parents (85.7%) and the patients (57.2%), themselves were concerned about fertility impairment and broached the issue with the oncologist (Goodwin et al., 2007).

In a survey conducted by Schover et al. , which was aimed at determining the knowledge, attitude and experience of male cancer patients regarding cancer-related infertility and sperm banking, showed that 51% of the respondents wanted children in the future, and the same percentage of them had been offered sperm banking. (2002a). But only 24% of men, however, eventually banked sperm. Lack of information was the most common reason for failing to bank sperm. Burns et al. conducted an exploratory cross-sectional survey on 50 female adolescent cancer patients and their parents by means of a questionnaire specifically developed for this purpose (2006). More than 80% were interested in pursuing fertility preservation techniques, but only 30% would be willing to wait one month or more

to start cancer treatment due to any fertility preservation procedure. Adults and adolescents had 70% agreement in their responses on fertility preservation and there was no statistically significant disagreement between them.

As with other potential complications of cancer treatment, all health care providers have a responsibility to inform patients about the risks to fertility with the treatment regime being given to them and the existence of different methods to preserve fertility. Referrals to reproductive specialists and psychosocial counselors should be made as soon as diagnosis of cancer is made and before embarking on any treatment which can reduce fertility. Psychosocial counselors and social workers can assist patients and families in the decision-making process about fertility preservation and make them understand that fertility preservation does not diminish the chance of successful cancer treatment. For men, the most common and successful option is sperm banking either from the ejaculate or testicular tissue. Other experimental options exist, if sperm banking is not a viable option and these include testicular tissue freezing in pre-pubertal boys. For women, the most established options are embryo and oocyte freezing and ovarian transposition. Embryo and oocyte freezing need ovarian stimulation for nearly 10mdays before oocytes are retrieved which re ether frozen as it is or are fertilized with sperm to generate embryos, which are frozen subsequently. Though the result of ovarian tissue freezing have improved and is becoming one of the commonest methods for fertility preservation in females it is still thought to be investigational. Transvaginal retrieval of immature oocytes with in vitro maturation (IVM) of oocytes, ovarian suppression with GnRH analogs and ovarian transplant are still experimental options. These options vary depending on the patient's age, the time available, type of cancer and whether the likelihood of ovarian involvement is high.

Thus with advances in the treatment of cancer and other life-threatening diseases, the number of young survivors with impaired fertility is growing and these affected patients and their families are interested in information about fertility issues and are in favour of fertility preservation. At present, however, only some of them receive information prior to treatment for various reasons. Today fertility preservation is far from being accessible to all, and not all health professionals have adequate knowledge and sufficient communication skills to counsel the concerned patients in a timely and supportive manner. Information transfer is challenging in this situation, and emotional support is demanding in this ethically and emotionally complex field, in which different issues have to be broached in the short time period between diagnosis and commencement of treatment. This requires multidisciplinary approach, which includes a fertility specialist, oncologist and a counselor who can help the patient in decision-making in fertility issues and fertility preservation.

The other issues that need to be addressed are risk of pregnancy to cancer as well as safety of pregnancy after cancer treatment. Though data is limited, but there seems to be no increased risk of cancer recurrence from fertility preservation methods or pregnancy, even in hormonally sensitive tumors. Similarly, many patients worry about the risk of passing cancer to their children. Apart from hereditary genetic syndromes and in utero exposure to some chemotherapy treatments, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increases the risk of cancer or congenital abnormalities in the children born after fertility preservation.

iv. WHO ARE THE CANDIDATES FOR FERTILITY PRESERVATION?

Cytotoxic chemotherapy and/or radiation therapy have been used to treat not only patients with malignant conditions, but also those with various nonmalignant systemic diseases. Patients who are under the risk of developing future ovarian failure may all benefit from fertility preservation technologies. There is a growing list of diseases in which the treatment, or the disease itself, is associated with gonadal damage. Some of these are- Childhood cancers, Breast cancers, cancer of the cervix, benign ovarian diseases, patients receiving Haematopoetic stem cell transplantation, patients receiving pelvic radiation, patients being offered prophylactic oophorectomy,

v. ETHICAL AND LEGAL ISSUES IN FERTILITY PRESERVATION

Fertility preservation can raise several ethical and legal issues, which should be addressed before such procedures are implemented. It should be made clear to all patients undergoing fertility preservation that fertility may not be restored despite attempts to preserve fertility has been made and that there is no guarantee that it will not have undue adverse effects in either the patient or any subsequent offspring. Given that some diseases are heritable, a genetic counselor should be available to discuss any potential risks of transmission of the disease to the resulting offspring and available genetic testing.

Apart from medical, genetic and psychological counseling financial counseling is also a must. One needs to discuss the cost involved in fertility preservation and whether insurance providers cover it. If available counseling regarding available funding and flexible strategies for dealing with issues relating to cost should also be provided.

Moreover a valid consent should be taken before these procedures. In case the age of the patient is less than 18 years, consent of the parent or guardian is essential. In patients who elect to cryopreserve gametes, embryos, or tissues, it is important to discuss the disposition in the event of death and this should be documented. Both health professionals as well as patients and their parents have knowledge and information deficits when it comes to fertility preservation and this warrants professional counseling with counselors having knowledge of fertility preservation.

Counseling of patients pursuing fertility preservation should include a discussion of all methods of fertility preservation as well as alternatives, such as the use of donor gametes, donor embryos, surrogacy and adoption. The patient's current state of health must be considered, as some individuals with severely debilitating cancers may be too ill to safely undergo fertility- preservation procedures.

The challenges the patient faces while making the decision is existential crisis about self, survival, and future, time constraints, access to care and financial constraints. Awareness of oncologist both medical and surgical on different fertility preservation techniques along with an experienced ART team to offers a full array of fertility-preservation techniques on short notice is very essential.

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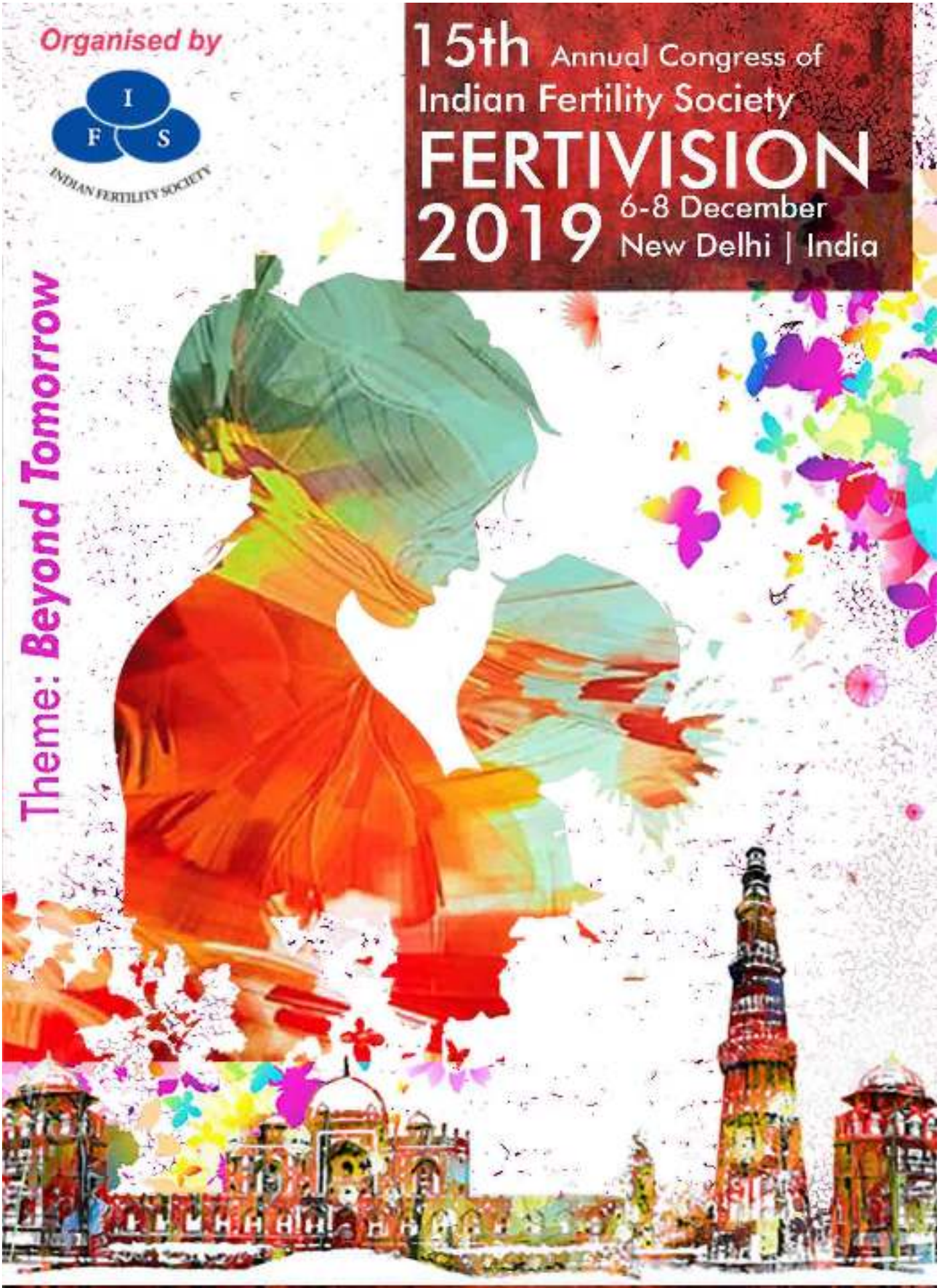

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