Overview of fertility preservation: History, management, available strategies and future directions in the Philippines

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ABSTRACT

Background: The increasing number of young survivors after cancer treatment and of patients with non-malignant conditions who are at risk for subfertility has resulted in a demand for fertility preservation services, including the Philippines.

Objective: The aim of this paper is to provide an overview of the history, indications, and management principles of fertility preservation. Also, the available strategies in the Philippines in both pre-pubertal and post-pubertal men and women and future directions of the field in the country will be discussed.

Materials and methods: Literature review, historical accounts

Results and conclusions: Fertility preservation should be a priority when treating children and adults of reproductive age with agents that have deleterious effects on the gonads. If harmful treatment will be used, the options of fertility preservation should be discussed, as early as possible by the primary physician in collaboration with the oncologist and the reproductive medicine specialist. Most of the known options for fertility preservation are available in the Philippines and are being implemented in the local IVF centers. Recent developments hint of a potentially faster progress in the field with the establishment of the Philippine Society for Fertility Preservation in collaboration with other professional societies and a linkage with the Department of Health with the signing into law of the National Integrated Cancer Control Act of 2019.

Keywords: Fertility preservation, embryo cryopreservation, gonadotoxicity, oocyte cryopreservation, ovarian tissue cryopreservation

INTRODUCTION

Fertility preservation (FP) is the application of various procedures to preserve the chance for genetic parenthood among those at risk of sterility in both men and women.[1] During the past decade, a wide range of medical conditions and social backgrounds that require fertility preservation procedures have been included.[1] However, it is the rising number of young cancer survivors during the past four decades that has served as its main driving force, drawing attention towards this rapidly evolving field.[2-3] This increase in cancer survivors[2,3] and the parallel advances in reproductive medicine have elevated fertility preservation into a unique discipline. With more patients expressing a demand for fertility after surviving cancer, practitioners in oncology, reproductive medicine, the social sciences, law, education, and the humanities have collaborated to develop interventions and protocols to help this unique subset of patients.[2,3] Furthermore, the same technologies are being used preemptively to overcome the effects of ovarian ageing, endometriosis, certain genetic diseases, and others.[1] This worldwide movement has reached the Philippines, requiring a review of fertility preservation in the local context.

Fertility Preservation: The Early Beginnings

The common element of most fertility preservation procedures is the storage of reproductive cells and tissues using freezing techniques. The original breakthrough happened in the 1950s using glycerol as a cryoprotectant and 'slow freezing' of human semen was then carried out in sperm banks[4]. Female patients, on the other hand, had few options for fertility preservation until the process of in vitro fertilization was established in the late 1970s when embryos were frozen by 'slow technique' as well.[1] Oocyte freezing and banking followed soon after. However,

because of the significantly poorer oocyte quality and survival after thawing[5], embryo cryopreservation became the preferred mode of fertility preservation over egg freezing. When vitrification, or ultra-rapid freezing, was developed, much of the chill injury and ice crystallization associated with slow freezing was avoided[6] and it was soon accepted as the preferred freezing technique for embryos[6], oocytes[7], and much later, ovarian tissues[8]. All these evolved during the last 3-4 decades when steady advances in reproductive medicine happened in the era of assisted reproductive technology (ART)[3].

At around the same time, parallel developments were happening in the field of oncology. In 1971, the National Cancer Act marked the start of the 'war on cancer'[3]. This allowed more aggressive and advanced treatments of cancers, resulting in a significant rise in the number of cancer survivors in the coming decades[1-3]. These findings were consistent with the trends in other countries.[9,10] With more young patients surviving various malignancies, the demand to address infertility after cancer therapy came into focus. In 2006, the American Society of Clinical Oncology (ASCO) and the European Society of Clinical Oncology (ESCO) came out with their first clinical guidelines about fertility preservation[11,12]. Among the key messages was that oncologists should discuss with their patients that cancer treatment may impair their future fertility and that a referral to the fertility specialist should be done to discuss options before their cancer treatment[11,12]. Several prominent international groups took up the cudgels in leading the charge: FertiPROTEKT in 2006 (Germany)[13], the Oncofertility Consortium in 2007 (Northwestern University, USA)[13], and the International Society for Fertility Preservation in 2008 (Belgium)[14]. Apart from these, regional and national societies that focused purely on fertility preservation began to form. These included the Asian Society for Fertility Society in 2016 (Vietnam)[15] and subsequently, the Philippine Society for Fertility Preservation in 2019 (Makati City).

Emergence of Fertility Preservation in the Philippines

Locally, progress in the fields of reproductive medicine and oncology were developing separately. Experts in fertility began to offer services in assisted reproductive technology (ART) in 1996 while various oncology practitioners implemented advances and state-of-the-art technology in their own subspecialties. As the international fertility preservation movement became organized, the activities in the local front were limited to individual doctors' exposures to international and local congresses. There was hardly any regular collaboration between gynecologists and oncologists in the management of young cancer patients.

The first organized attempt to institutionalize fertility preservation in the Philippines happened in August 2015 when a group of fertility specialists and scientists from the Center for Advanced Reproductive Medicine and Infertility (CARMI) of St. Luke's Medical Center Global City went to St. Marianna University Hospital in Japan for short-term training in ovarian tissue cryopreservation (OTC) and transplantation. This author along with three other fertility specialists and one embryologist headed this group. Their training was conducted under Professor Nao Suzuki, chair of the OB-GYN department and Dr. Seido Takae. Prof. Suzuki, a gynecologic oncologist, is the President of the Japanese Society for Fertility Preservation and a pioneer in OTC. Dr. Takae is a reproductive medicine specialist and is an expert in ovarian tissue cryopreservation.

When the group returned to the Philippines, the St. Luke's Medical Center Global City created the Committee on Fertility Preservation. This marked the first local group of doctors from various disciplines formed particularly for patients requiring fertility preservation. Early during the following year, CARMI organized the first local Ovarian Tissue Cryopreservation and Transplantation workshop that was conducted by the St. Marianna University group where special lectures by Prof. Suzuki, Dr. Takae, and Professor Claus Yding Anderson of Denmark, another world icon on OTC, were delivered. Representatives from local and regional ART centers attended the workshop.

When the First Asian Congress of Fertility Preservation opened in Vietnam in 2016, it marked the inaugural meeting of the ASFP with Prof. Suzuki as founding president. Suzuki appointed this author as the Philippine representative to ASFP and also as a member of the inaugural Board. Later in the same year, the first two cases of ovarian tissue cryopreservation in the Philippines were reported[16]. In March 2018, the first Fertility Preservation Symposium was held as a joint activity of St. Luke's Medical Center Quezon City and Global City where different specialists contributed to the one-day course. It was a collaborative effort among multidisciplinary specialists from the two St. Luke's hospitals.

In early 2019, in partnership with the St. Luke's Medical Center Global City, the Asia Pacific Initiative on Reproduction (ASPIRE) organized in Taguig City a Male Infertility Master Class that included a workshop on Testicular Tissue Cryopreservation. Later in the same year, during the inaugural Philippine Society for Fertility Preservation (PSFP) Congress, the local society was officially formed with the induction of 182 founding members composed of reproductive medicine specialists, various oncologists, embryologists, urologists, and general obstetrician-gynecologists.

INDICATIONS AND BASIS

Oncologic Conditions

The bulk of patients treated for fertility preservation belong to this category. With increased cancer survival, more young patients will expect to live longer and where fertility becomes an important issue[17]. Woodruff estimates that 10% of all new cancers diagnosed annually are below 45 years old and many of who may require fertility preservation services[3,18]. According to the Global Cancer Observatory, there were over 14,000 (6,200 male and 7,901 female) new cancer cases in the Philippines in 2018 that potentially required fertility preservation services[19]. This is similar to the estimate of 16,000 new cancer cases below 40 years old by the group of Laudico in 2015[20].

Understanding the long-term effects of cancer treatment provides the basis of FP procedures. The gametes of both men and women are sensitive to the effects of chemotherapy and radiotherapy, with gonadal failure being a real possiblility[1,21,22]. Although the functional recovery will be dependent on the patient's age, type of therapeutic agent, and the treatment dose delivered[21,22], it may still be difficult to predict the degree of gonadal damage[1]. But there are certain principles that have been established. One is that the chance of inducing premature ovarian failure (POF) is dependent on the available ovarian reserve at the time of treatment, suggesting that gonadotoxic treatment given at an advanced age is more likely to cause POF than those given at a younger age[23]. Another principle is that there are certain chemotherapeutic agents or radiation doses that can cause total irreversible gonadal damage[24,25]. Finally, there are certain cancer therapies that result in minimal or no effect on gonadal function[24,25]. (Table 1).

Non-Oncologic Conditions

There are non-oncologic conditions that have been suggested as candidates for fertility preservation. Their risk stems from immunosuppressive therapy, chemotherapy, and development of severe chronic complications or natural disease progression. This group includes patients with autoimmune diseases, those anticipating hematopoietic stem cell transplantation, medical conditions causing premature ovarian failure (POI), genetic disorders, and men with severe testicular damage or severe body trauma[26]. Martinez summarizes the non-oncologic conditions that may require fertility preservation (Table 2)[26]. More recently, women with BRCA gene mutations were shown to have decreased fertility and fertility preservation options were suggested to overcome this difficulty[27].

Table 1. Chemotherapeutic drugs according to gonadotoxicity level (Adapted from Mintziori et al Maturitas 2014; 77: 85-89)

Risk Category	Chemotherapeutic Drugs
High	Cyclophosphamide, Chlorambucil, Melphalan, Busulfan, Nitrogen mustard Procarbazine, Dacarbazine, Ifosfamide, Thiotepa, Carmustine, Lomustine
Moderate Risk	Cisplatin, Carboplatin, Doxorubicin, Etoposide
Mild or None	Bleomycin, Actinomycin D, Vincristine, Methotrexate, 5-Fluoro-uracil, Mercaptopurine, Prednisone, Interferon-alpha

Table 2. Non-oncologic conditions requiring fertility preservation (Adapted from Martinez et al. Fertil Steril 2017; 108:407-15)

Indication	Disease
Autoimmune Diseases	Systemic lupus erythematosus (SLE), Behcet's disease, Churg-Strauss syndrome (eosinophilic granulomatosis), Steroid resistant glomerulonephritis, Granulomatosis with polyangitis (formerly Wegener's granulomatosis), Inflammatory bowel disease, Rheumatoid arthritis Pemphigus vulgaris
Hematopoietic stem cell transplantation	Autoimmune diseases unresponsive to immunosuppressive therapy Hematological diseases (sickle cell anemia, thalassemia major, plastic anemia)
Medical conditions causing POI	Altered hypothalamic-pituitary-gonadal axis, ovarian oophoritis, benign ovarian tumors, Galactosemia, Beta-thalassemia, Endometrisosis
Genetic disorders	Klinefelter syndrome, Mosaic Turner's Syndrome, Fragile X mental retardation, BRCA gene mutation
Severe Body Trauma requiring surgical intervention	
Testicular damage	

Social Reasons

There are a few circumstances why fertility preservation has been proposed for social indications. Among women, oocyte cryopreservation for non-medical purposes or 'social egg freezing', developed because of two groups: single women without a partner but would like to be assured of future fertility and busy women, either

single or married, who elect to postpone motherhood for professional or reasons of opportunity[28]. Regardless, although certain societies abroad have cultural qualms, there are no moral nor ethical issues against social egg freezing in the Philippines apart from the full disclosure of the advantages, disadvantages and expectations of the process especially for those in advanced age[29]. Among men, elective sperm freezing has been carried out for various reasons such as those planning gender reassignment procedures, those in hazardous occupations as in the military, and those severely ill who are anticipating death in the near future[29,30]. For some of these cases, the posthumous use of sperm for reproductive purposes is usually allowed only with a written instrument detailing the consent[29,30].

DIAGNOSIS, PREDICTION AND RISK ASSESSMENT

The importance of diagnosing and prognosticating the chance for gonadal failure can never be overemphasized. For patients facing gonadotoxic chemotherapy and/or radiotherapy, clinicians will need to rely on biomarkers that may reasonably predict future fertility apart from the details of the therapy itself[25].

Among women, the most useful markers are anti-Mullerian hormone (AMH), sonographic antral follicle count, follicle-stimulating hormone (FSH), and inhibin B[25]. AMH is regarded as the most reliable. It is produced in the granulosa cells of nearly all stages of follicular development, including those that are not FSH-dependent[31]. Like AFC, AMH is an excellent predictor of ovarian reserve but is more objective unlike AFC. This is because AFC is operator-dependent with a high inter-observer variability[31]. AMH demonstrates a rapid decline soon after the start of all chemotherapeutic agents and its recovery pattern is a reflection of the degree of toxicity of the regime used[30,31]. FSH in combination with inhibin B is a promising biomarker to predict post-treatment ovarian damage in pre-pubertal girls[32].

PRETREATMENT COUNSELING

Pretreatment counseling is imperative. The 2018 ASCO guidelines states that health care providers should initiate the discussion on the possibility of infertility as early as possible, discuss fertility preservation options, and must refer all potential patients to appropriate reproductive specialists[34]. For children and adolescents, it has been estimated that greater than 80% diagnosed with malignancy will survive the disease[33], so that a discussion of the harmful effects of treatment on fertility must be carried out with the parents or guardian. The treatment plan must include a discussion of the long-term reproductive possibilities[24].

Similarly, all adult men and women of reproductive age should be thoroughly informed about the risks of treatment and available options for fertility preservation before the initiation of any gonadotoxic treatment[34]. Close communication between the patient and the multidisciplinary team must be implemented so that a clear therapeutic plan is reached. This is especially true in women where the procedure is likely to be more invasive and costly compared to men where freezing a semen sample may be enough[24]. This plan must consider issues such as the patient's age and wishes, and the timing of the FP strategy with the cancer treatment. Conservative 'fertility-sparing' surgery for women with gynecological malignancies must be discussed when appropriate[35].

TREATMENT STRATEGIES

Options for Women

Although the fertility preservation options for women of reproductive age have been recently proposed, some of these strategies have been part of the standard procedures in assisted reproductive technology (ART) while new methods are undergoing evaluation. There are established and experimental strategies that compose the many evolving options in fertility preservation for women.

Established procedures

The cryopreservation of embryos is a well-established strategy of fertility preservation. It provides satisfactory live birth rates after 'emergency' in vitro fertilization (IVF) before gonadotoxic therapy is given[36]. To shorten the waiting time before definitive cancer treatment, 'random-start' or 'luteal phase start' ovarian stimulation is can be utilized to produce oocytes than can subsequently be fertilized and stored after freezing[36,37]. To minimize estrogen stimulation in hormone receptive cancers such as breast malignancy, letrozole or tamoxifen, may be used during ovarian stimulation[37]. Individualized assessment is the key for optimum ovarian stimulation. However, the main drawback of this option is the two-week requirement for follicular development and egg retrieval, which may or may not delay cancer treatment[37].

The most suitable strategy for young single women without a male partner is the cryopreservation of unfertilized oocytes following the same principles of ovarian stimulation for embryos. The collection of unfertilized oocytes must be completed before gonadotoxic cancer therapy although women should expect fewer oocytes after ovarian stimulation compared to healthy controls[38]. The concept of 'social egg freezing' is of great interest to many single women of advancing reproductive age and those who wish to delay motherhood, but most

studies suggest that these are best done below the age of 38.[39] For all indications of oocyte cryopreservation, the recommended freezing technique is vitrification, an ultra-rapid type of cryopreservation that is the currently accepted method of freezing. The landmark study of Rienzi et al that showed comparable live birth rates of sibling oocytes that were frozen-thawed compared to fresh embryos marked the acceptance of oocyte freezing as an accepted scientific procedure[40].

The latest FP strategy that has been upgraded from 'experimental' to 'established' is ovarian tissue cryopreservation (OTC)[8]. For young women with cancer, OTC is considered a reliable option but can only be done in specialized centers. Because the retrieval of the ovary or ovarian tissue can be immediate without the need for ovarian stimulation, OTC is the method of choice for patients with limited time before cancer therapy. Recent data from specialized centers indicate very acceptable pregnancy rates after ovarian tissue transplantation[8]. Furthermore, OTC is the only method to preserve fertility for pre-pubertal girls because ovarian stimulation and IVF are not possible[8]. However, it must be considered that there is a risk of reintroducing malignancy through the tissue of a cancer patient[41,42]. The risk of cancer reseeding from ovarian tissue is highest for leukemia compared to other cancers[41,42]. Therefore, in considering OTC for hematologic cancers, it must be assured that there is minimal residual disease before transplantation is carried out[42]. To overcome this drawback, new methods are being developed to detect cancer cells in the ovaries and ovarian tissues prior to transplantation[43].

Some of the established strategies were already being implemented before the global fertility preservation movement took place. Fertility-protecting procedures in radiotherapy included gonadal shielding and ovarian transposition (oophoropexy)[44]. 'Fertility-sparing' conservative surgery for early stage disease in cervical, endometrial and ovarian cancers have been performed during at least the past two decades.[44]

Experimental procedures

There are a number of fertility preservation strategies that are considered experimental essentially for the lack of good evidence. Among the most popular 'experimental' options is the co-administration of GnRH–agonists for ovarian protection during gonadotoxic chemotherapy. Recent meta-analyses evaluating GnRH agonists in breast cancer patients have found an overall decreased risk of premature ovarian failure[45,46]. But the evidence is still low, and the most recent statement from the ASCO states that GnRH agonists 'should not be used in place of proven fertility preservation methods' and that 'in the setting of young women with breast cancer, GnRH agonists may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency'[34].

Other strategies currently undergoing evaluation for their efficacy in fertility preservation procedures include whole ovary transplantation, in vitro maturation (IVM) of oocytes, the use of existing stem cell in the ovary, and micromanipulation strategies on the oocyte or zygote. Some of these strategies have some ethical issues to be resolved.[26]

Options for Men

Established

By far, the cryopreservation of sperm after masturbation is the most performed and the most established method of fertility preservation in men. As the usual method of choice, it is the ideal method for men with normal to severe sperm problems because of the ease of collection and its low cost. When collection by masturbation is not possible, other techniques as penile vibratory stimulation and electro-ejaculation may be utilized[47]. For men with very severe oligoasthenoteratospermia (OAT) or azoospermia, sperm collection may be accomplished through various techniques of surgical sperm retrieval that have been developed[47]. These include such methods as micro-epididymal sperm aspiration (MESA), testicular sperm aspiration (TESA), testicular sperm extraction (TESE), and microsurgical testicular sperm extraction (micro-TESE), all of which were developed at around the time when intracytoplasmic sperm injection (ICSI) was discovered[47]. Sperm should ideally be collected prior to treatment, as chemotherapy and radiotherapy may cause genetic damage or gonadal failure.

The use of scrotal shields to protect the gonads from irradiation for pelvic or proximal thigh malignant disease is also practiced[48,49].

Experimental

There are only a few experimental methods of fertility preservation for men. The most popular is testicular tissue cryopreservation, which has limited use in adults but is the only option for pre-pubertal boys[50]. However, even though it is considered experimental, there is increased use in recent years[51]. Testis xenografting is in its early experimental stages with little available data[52]. Hormonal therapy in men is considered ineffective in preserving fertility[34].

Available Options in the Philippines

All established strategies of fertility preservation for men and women are available in the Philippines. Fertility-protecting procedures during radiotherapy and fertility-sparing surgery in early gynecologic cancer are usually performed by qualified clinicians in their respective

hospitals. However, the provision of embryo, oocyte, ovarian tissue, and sperm cryopreservation requires the availability of an IVF center. A quick look at the distribution of the six (6) IVF centers within the country shows that at least one facility is present in each of the three island groups of Luzon, Visayas, and Mindanao (Figure 1). However most are concentrated in Metro Manila, and suggests that additional centers are required in strategic areas to accommodate the other potential needs for fertility preservation services in the country.

As far as available strategies requiring ART facilities are concerned, the established and two of the available experimental methods that are offered in the Philippines are presented, detailing the availability of the service in the IVF facilities (Table 3). It is important to note that only half of all IVF centers offer services for ovarian tissue cryopreservation which is the service that is most inquired recently. Of the available experimental methods, only three (3) centers offer testicular tissue cryopreservation services, with a minority giving out services for IVM. Following the earlier principles discussed, Figure 2 shows the scheme of management for fertility preservation for women in the Philippines based on the available methods. Similarly, the management scheme for pre-pubertal and pubertal boys is presented in Figure 3, noting that half of the IVF facilities in the country do provide testicular tissue cryopreservation.

The issue of access to fertility preservation services at the current time becomes crucial given the limited availability of IVF facilities in the country. Those who require embryo, oocyte or sperm cryopreservation have no choice but to go to the IVF centers because of the required specialized expertise and facilities for ovarian stimulation, monitoring, oocyte retrieval, fertilization (if needed) and the cryopreservation process itself. However, ovarian tissue cryopreservation need not be done completely at the IVF centers. Whole ovary specimen may be retrieved by laparoscopy in the local hospital and is immediately transported in sterile saline solution with ice in an insulated container. The specimen must reach the IVF facility within 24 hours for immediate processing for best results. This process follows the referral system of the ovarian tissue cryopreservation program in Denmark where the ovary is harvested at a local site and immediately transported under special conditions to regional or central referral sites[53].

FUTURE DIRECTIONS

In early 2019, the program for fertility preservation got a boost when the National Integrated Cancer Control Act (2019) was signed into law and fertility preservation was included among its programs[54]. Following the model

Figure 1. Geographical distribution of the six (6) IVF centers in the Philippines

Table 3. Current availability of fertility preservation services in the local IVF centers (With permission)

	Method	CARMI	Kato	Victory ART	CARE	Repro Optima	Davao IVF
ESTABLISHED	Embryo & Oocyte cryopres	✔	✔	✔	✔	✔	✔
	Ovarian Tissue cryopres	✔	-	-	✔	✔	-
	Semen cryopres	✔	✔	✔	✔	✔	✔
	Surgical Sperm Retrieval	✔	✔	✔	✔	✔	✔
EXPERI-MENTAL	Testicular Tissue cryopres	✔	-	-	✔	✔	-
	IVM	-	✔	-	✔	-	-

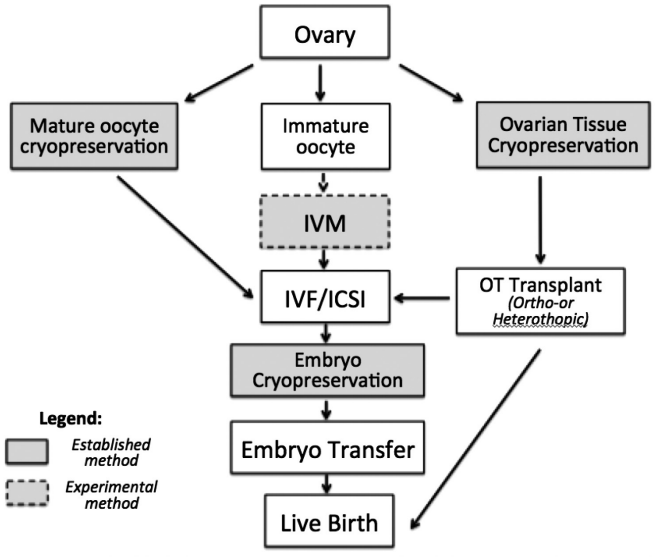

Figure 2. Scheme of fertility preservation for women following available options in the Philippines (Adapted from Martinez et al Fertil Steril 2017; 108:407-15)

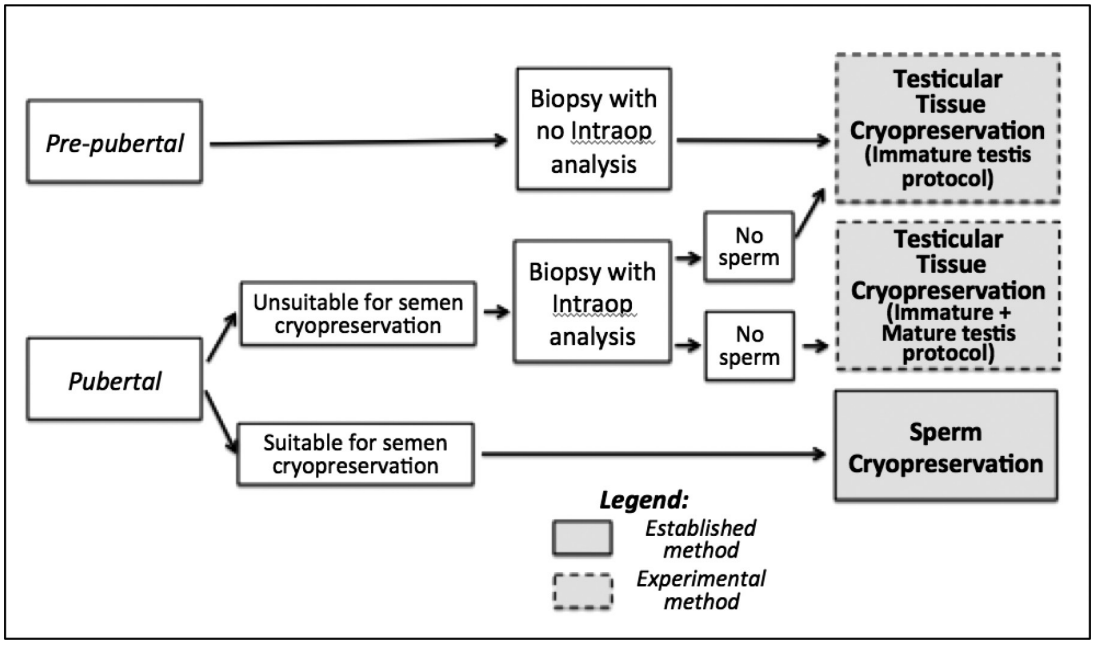

Figure 3. Fertility preservation scheme for pre-pubertal and pubertal boys following available options in the Philippines (Adapted from Martinez Fertil Steril 2017; 108:407-15)

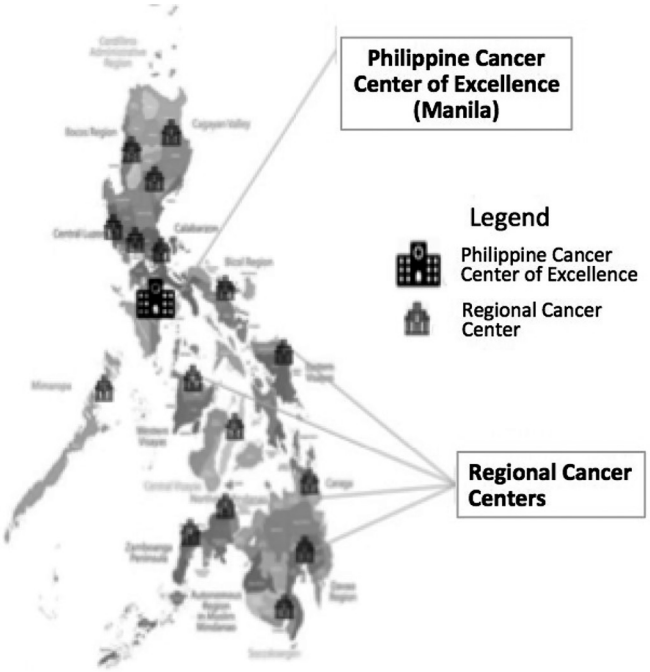

Figure 4. Vision for the Philippines in the National Integrated Cancer Control Act of 2019: Proposed distribution of regional cancer centers and the central Philippine Cancer Center (Cairo C, 2019, Oral communication)

where regional cancer centers all over the Philippines would be set up (Figure 4), parallel regional IVF centers serving these cancer centers must also be established[54].

Finally, with the formal organization of the Philippine Society for Fertility Preservation, various projects are lined up. Much of the short-term goals are centered on education and awareness campaigns that focus on the basics of fertility preservation. Separate activities involving health professions, patients, and the general public have been drawn. Many of these would be held in collaboration with the involved professional medical societies in oncology, reproductive medicine, urology and obstetrics-gynecology including non-government organizations. Cross linkages between all these groups and societies must be developed. Improvements on the knowledge about local fertility preservation will also be promoted through a registry of cases and clinical research. Ultimately, the long-term goal is to have a national fertility preservation program with smooth coordination between the involved subspecialties and available public and private facilities to meet the needs of all Filipinos.

SUMMARY AND CONCLUSIONS

The global movement of fertility preservation has reached the Philippines. Local health care providers need be aware of the management principles and strategies, both the established and the experimental, to be able to meet the increasing demands of young oncologic and non-oncologic patients. The primary physician must band with the oncologist, reproductive medicine specialist, and the paramedical support team to be able to provide a thorough and holistic management to this delicate set of patients. ■

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