Fertility preservation: moving ahead faster than expected!

Pedro Barri • Antonio Pellicer

Published online: 18 January 2014
© Springer Science+Business Media New York 2014

The III World Congress of the International Society of Fertility Preservation (ISFP) was held in Valencia November 7th–9th, 2013. There was a substantial number of registrations (453) as compared to the previous meeting in 2011 with delegates from 47 countries, showing the worldwide increasing interest in this field.

The first session was devoted to the damage of cancer treatment to the genital tract. Norah Spears (UK) presented her experiments evaluating cellular apoptosis and showing that the mechanism by which chemotherapy induces follicular loss is a “burn out” effect by which primordial follicles grow and disappear, rather than a direct effect of chemotherapy on the primordial follicular pool.

Richard Anderson (UK) analyzed cancer-induced changes in the testes and spermatozoa. It was shown that before chemotherapy in men with Hodgkin disease and testicular cancer there is already DNA damage in sperm. Moreover, after treatment, DNA damage is higher than in control patients, but it is repaired with time. The same is true for sperm aneuploidy. It is higher after chemotherapy, but recovers 18 months after treatment finishes. Neither radiotherapy (relative risk, RR, 0.8), nor chemotherapy (RR 1.2) is associated with increased risk of malformations in the newborn infant of these men as fathers. A recent study has shown that the rate of congenital major malformations is 3.7 % in men after cancer

treatment as compared to 3.2 in controls. Most of these malformations came from fathers who tried conception shortly after cancer treatment.

Hamish Wallace (UK) addressed the issue of counseling young female patients with cancer. He emphasized how important it is to spend time with the patient and her family in counseling, taking into consideration the probability of total infertility after cancer treatment. Specially important to the ovaries is radiotherapy in children/prepubertal girls because 19 Gy induce sterilization at 7 years of age. However, 11 Gy are only fatal to the gonad at 42 years. Then, ovarian tissue cryopreservation becomes a real alternative in these very young women. The uterus might be also affected. In fact, the volume of the uterus is decreased after radiotherapy and more complications of pregnancy have been described. However, experience in oocyte donation programs does not sustain the notion that the endometrium becomes non-functional after radiotherapy.

Kirsten T. Schmidt-Macklon (Denmark) analyzed the probability of spontaneous recovery of ovarian function after cancer treatment. She showed that the probability of having children is as high as 83 % if the cancer survivor has menses at age 20 years. She followed 191 women in whom an oophorectomy was performed to preserve their fertility in case the remaining ovary would be completely depleted of gametes. Of a total of 143 who replied to the questionnaire sent by the investigators, 48 had children spontaneously (34 %). In most of the patients with leukemia needing bone marrow transplantation, ovarian failure was detected (87 %). However, in most of the patients with breast cancer, ovarian function remained intact (85 %).

In session 2 fertility-sparing surgical strategies were discussed. Michel Roy (Canada) presented his experience with conservative treatment of cervical cancer Ia1, Ia2, Ib1, <2 cms and with limited endocervical involvement. The technique applied was a vaginal radical trachelectomy (VRT)

Capsule This introductory article summarizes the most important messages from the World Congress on Fertility Preservation.

P. Barri
Department of Obstetrics, Gynaecology and Reproduction, Institut
Universitari Dexeus of the Universitat Autònoma de Barcelona,
Barcelona, Spain

A. Pellicer (✉)
Instituto Valenciano de Infertilidad (IVI) and Hospital Universitario
La Fe, University of Valencia, Valencia, Spain
e-mail: apellicer@ivi.es

combined with laparoscopy for sentinel node evaluation and additional lymphadectomy if necessary. He presented a series of 924 cases with 4.4 % of recurrences and 1.6 % deaths. A total of 106 pregnancies were followed with a 20 % of miscarriages, 4 % of deliveries <31 weeks, 14 % 32–36 weeks and 55 % of deliveries occurred after 37 weeks of gestation.

Jacques Donnez (Belgium) presented Philippe Morice's, experience, who was unable to attend, on the conservative treatment of borderline ovarian tumours. The accumulated worldwide and personal experience is reassuring with evidence that allows us to recommend to perform conservative fertility sparing surgeries in these cases. The decision of cystectomy or ovariectomy will depend on the size, type of tumours and bilaterality. ART is accepted for these patients if a pregnancy has not been achieved naturally. Rate of recurrences is acceptable and the vast majority will also be borderline without life risk for the patients.

Conservative treatment of endometrial cancer was presented by Pedro N. Barri (Spain). He showed the requisites that a patient must fulfill to be treated conservatively. There is a consensus on the protocol of gestagens to be used: a daily dose of 500 mg of medroxyprogesterone acetate (MPA) or 150 mg/day megestrol acetate (MA) for 6 months although intrauterine release of progestins can also be proposed. Around 15 % of the patients do not respond and 85 % will present a remission at 6 months. However 20–30 % will present recurrences that can also be medically treated with good results. Overall survival with these protocols is excellent, ART can be helpful and a hysterectomy is mandatory when the family project is complete. More than 600 cases are recorded in the literature with a pregnancy rate that ranges from 35 to 40 % with normal clinical outcome of these pregnancies.

Gonadal medical protection to chemotherapy was presented by Dror Meirow (Israel) who showed some discordant studies published so far with the use of GnRH agonist for this purpose. He suggested studying new molecules (Imitab, S1P, AS 101, PFA) that can block the different pathways (PI3K/PTEN) of follicular activation avoiding the final depletion of the ovarian reserve. So far, preliminary results are very promising.

Session 3 was devoted to technical aspects of ovarian cortex transplantation. Tommaso Falcone (USA) emphasized the relevance of advising patients before surgery that spontaneous pregnancy may perfectly occur after treatment because ovarian function is not lost. Orthotopic transplantation is preferred to heterotopic because spontaneous pregnancies can occur. But a pregnancy employing IVF has been recently reported from Australia after heterotopic transplantation of the ovary in the abdominal wall (although very close to the peritoneum). Ovarian function recovers 4.5 months after transplantation, as mentioned by Sherman Silber (USA), and implanted ovarian tissue can be functional 4–5 years.

Claus Yding Andersen (Denmark) challenged the audience with an hypothetical indication for ovarian tissue freezing: to

delay menopause and to avoid/delay as much as possible the use of hormone replacement therapy. Ideally would be indicated in women undergoing surgery for other reasons, such a cesarean section, in whom a small portion of ovary is removed, cryopreserved and replaced when the ovaries start to fail. The concept is based on the fact that, removing part of or the entire ovary, only advances menopause by 1.2 years, and also because this type of surgery does not decrease the chance of pregnancy in women who have had an ovary removed. He considered that, given the increase in life expectancy, a strategy that prolongs the endocrine function of women might be beneficial.

Marie Madelaine Dolmans (Belgium) addressed the issue of the risk of transplantation of malignant cells when performing procedures of fertility preservation. She showed their studies in women with leukemia in whom the risk is higher, although the first cycle of chemotherapy seems to be sufficient to kill potential malignant cells present in the ovaries. Also risky is non-Hodgkin lymphoma, in which 10 % of patients have a risk of ovarian contamination. Breast cancer does not seem to be an issue, unless fertility is preserved in women in advanced stages of the disease, which is probably a contraindication by itself.

Session 4 dealt with other clinical considerations in fertility preservation. R.C. Chian (Canada) presented his experience with natural cycle and in vitro maturation. Pregnancy rates ranged between 15 and 35 % with more than 5,000 babies born with this technique although miscarriage rates are excessively high. In case of fertility preservation, he suggested vitrifying oocytes after IVM and not before.

Kenny Rodriguez Wallberg (Sweden) confirmed the safety of ovarian stimulation protocols which combine aromatase inhibitors, gonadotropins and GnRH antagonists. It seems clear that with letrozole estradiol levels are lower, gonadotropin requirements are not increased and the number of oocytes and embryos is normal. No increase in tumour relapse has been observed in cancer patients treated with these protocols. Thanks to the efficacy of oocyte and embryo cryopreservation techniques, these strategies should be proposed to patients if they have enough time before starting chemotherapy.

Herman Tournaye (Belgium) presented his experience with male fertility preservation. He mentioned that although azoospermia is not always the final result of chemo/radiotherapy different strategies should be proposed to this young patients. The challenge is the management of prepubertal boys in whom testicular biopsy and freezing of testicular tissue is the only alternative available. For the future, we should also consider the possible use of artificial gametes.

Jane Ruman (USA) clearly showed that the access of oncologic patient to fertility preservation is limited everywhere with only 50 % of oncologists having knowledge and informing these patients properly. The final result is that in the USA only 4 % of oncologic patients have a fertility preservation strategy carried out.

Session 5 was devoted to methods of *in vitro* culture of oocytes and entire follicles in order to be able in the future to avoid transplantation of cancer cells in patients at risk, especially young women in whom ovarian cortex was removed at younger age. Evelyn Tefler (UK) described the experiments of her lab with entire follicles, grown from the primordial to the preovulatory stage. The culture starts by activation of primordial follicles; continues by isolation of growing follicles and then oocytes are removed from the follicular environment to continue growth and maturation *in vitro*. With the aid of somatic cells and growth factors, they have been able to obtain around 30 % of metaphase II oocytes. Development *in vitro* is much more successful in adult women than in girls.

Helen Picton (UK) showed her experience with long culture systems (>30 days) adding gonadotropins at physiological doses. These follicles contain oocytes that can reach the metaphase II stage.

Stine Gry Kristensen (Denmark) explored a different approach consisting in isolation of follicles from cortical tissue and the creation of artificial ovaries *in vivo* after encapsulation of follicles with alginate droplets into the renal capsule in rodents. While animal tissue provided interesting outcomes in terms of oocyte quality, experiments employing human tissue were not that successful.

Outi Hovatta (Sweden) compared two methods of ovarian tissue freezing: slow freezing and vitrification. The latter was associated with better stroma and vascularization, suggesting that vitrification can be the way to go in the near future. In fact, a pregnancy is ongoing after vitrification of the ovary and retransplantation. In this sense, Sherman Silber (USA) made clear that, according to his experience, slow freezing and vitrification both work well. There is not such a great difference between methods in tissue preservation as it has been observed in oocyte or embryo freezing.

Kate Hardy (UK) showed the relevance of AMH in inhibiting primordial follicular growth. Simultaneously, and employing k67 staining, she showed the intense proliferation potential of primordial follicles, and this might be the reason why they are so sensitive to chemotherapy. Using mathematical models they have been able to show that primordial follicles are located in clusters and have paracrine/intracrine functions to maintain growth inhibition among them. Also, she showed how important granulosa cells are for follicular and oocyte growth as compared to other groups that maintain the concept that the oocyte orchestrates all the events in folliculogenesis.

Several aspects were covered in session 6. Cesar Diaz (Spain) presented his study on the *in vitro* antileukemic treat-

ment of ovarian cortex with dexamethasone prior to transplantation. After analyzing the results obtained with 8 cases of acute leukemia, no significant improvement has been achieved.

Sam Kim (USA) informed about the risks of vitrification on the different TZP of gap junctions. Apparently, worse results were obtained with vitrification due to abnormalities in the DNA repair process and in the nuclear and cytoplasmic maturation.

Ana Cobo (Spain) clearly showed with very large studies that clinical results obtained with vitrified oocytes were identical to those obtained with fresh oocytes. No differences in neonatal outcomes were observed. Cumulative analysis of the data proved that oocyte to baby rate can be as high as 6,5 % per oocyte and that 20 oocytes can be necessary to have high pregnancy rates.

Pasquale Patrizio (USA) introduced the new technique of dry and freeze of biological materials using combinations of trehalose and sucrose for lyophilization. He also presented a new strategy of removing a whole ovary and performing a direct ovary perfusion and directional freezing with a special device in order to reduce vascular injury and follicular damage.

In session 7, two aspects of the future of fertility preservation were addressed. Gerald Schatten (USA) showed the experiments performed in his lab and others in which sperm and oocytes have already been created from immature stem cells. Moreover, pups have been born after employing this sperm to fertilize oocytes. Thus, an alternative source of germ cells can be readily available in the near future for people who survive cancer and have their gonads permanently damaged.

The final speech of the congress was given by Matts Brannstrom (Sweden). He has been well known for pursuing uterine transplantation in rodents and non-human primates. After many years of research, he was authorised to perform surgery in humans. He described a series of 9 women in whom uterine transplantation has been performed successfully and they are awaiting pregnancies after embryo replacement, since all of them underwent IVF and embryo freezing before uterine transplantation. Surprisingly, organ rejection has not been a major issue in this series. He also mentioned a case performed in Turkey in which the uterus is active and two pregnancies have resulted after embryo replacement in IVF. In both cycles the woman has miscarried. Thus, there is not a newborn infant after uterine transplantation yet, but Dr Brannstrom transmitted to the audience his hope that it will be a reality soon.