Female Fertility Preservation
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1. Abstract
The increasing incidence of malignant diseases that often require gonadotoxic treatment and the tendency to become parent later, results in an increased need for fertility preservation. The following review summarizes different options for fertility preservation addressed to pre-puberal girls and women at reproductive ages whose fertility has been compromised. The need for both oocyte and embryo cryopreservation andagination has been proposed as future clinical therapies for female infertility.

2. Materials and Methods
- Scientific literature search on PubMed based on specific words such as: fertility preservation, oocyte and embryo cryopreservation and so on. The research has been focused on recent papers and reviews.
- Assisted in a conference organized by Victor Grifols and Lucas Foundation about the 30th anniversary of the first child born in Spain after IVF.

3. Introduction
- Female fertility is based on a pool of non-growing follicles in the ovary, some of which start growing every day. This procedure becomes gonadotropin dependent and ends with ovulation.
- Female fertility preservation has become an interesting matter for society in the last time. This interest has grown due to the increasing rates of cancer in young population and the delay in childbearing for social issues (following diagram). Cancer treatments (in pre-puberal and fertile women) cause follicle loss which implies an alteration of reproductive potential.

4. Options to Preserve Female Fertility

- **Ovarian tissue cryopreservation**

  - **Procedure:** remove ovarian grafts (Fig. 3) and freeze them. When they are stored, tissues can be stored in order to use them in the future. Lately, ovarian tissues can be thawed and grafted to orthotopic or heterotopic site in the body. Strips have to restore ovarian endocrine function and return normal ovaries. The process of ovarian transplantation is long-term storage.
  
  - **Advantages:**
    - No ovarian stimulation is needed (Fig. 3).
    - No risk of reimplant malignant cells.

  - **Disadvantages:**
    - 1) Requires surgery.
    - 2) Risk of reimplant malignant cells.

- **Slow freezing**

  - **Procedure:** Used for embryo cryopreservation. Slow freezing protocols consist in cooling the samples by cooling rates (Fig. 4). In order to prevent intracellular ice formation and toxic concentrations of solutes the freezing solution must be supplemented with cryoprotective additives (CPA). Once embryos are in LN2, they can be stored for a long time.

  - **Indications:** addressed to women in reproductive age who want to delay motherhood or who have to be submitted on invasive treatment.

  - **Advantages:**
    - No surgical procedure.
    - No risk of reimplant malignant cells.

  - **Disadvantages:**
    - 1) Ovarian stimulation is needed.
    - 2) Not indicated for pre-puberal girls.

- **Vitrification**

  - **Procedure:** used for both embryo and oocyte cryopreservation. Consist in super rapid cooling procedure (Fig. 5) achieved by putting the samples in direct contact with LN2. The aim of vitrification is to prevent ice formation and too fast dehydration or cytolysis, that’s the reason why concentrations of CPA are extremely high.

  - **Indications:** addressed to women in reproductive age who want to delay motherhood or who have to be submitted on invasive treatment.

  - **Advantages:**
    - No surgical procedure.
    - No risk of reimplant malignant cells.

  - **Disadvantages:**
    - Ovarian stimulation is needed.
    - Not indicated for pre-puberal girls.

- **Embryo and oocyte cryopreservation.**

  These techniques consist in freezing the samples following different protocols according to their characteristics and storing them in LN2 for future applications.

  - **No all procedures can be used for all patients:** while ovarian tissue cryopreservation is more suitable for pre-puberal girls, oocyte and embryo cryopreservation is the main election for women at reproductive ages.

  - **Protocols about samples cryopreservation have been designed to prevent as much as possible cell alterations and death. Somatic cells for slow frozen oocytes are much lower than vitrified ones, that’s the reason why slow freezing oocytes has not been used anymore in clinics.

  - **Future goals on female fertility preservation are the improvements and optimization of current procedures.

  - **There are some researchers looking for new strategies, they believe that an ideal fertility preservation approach would prevent delays in coming year saving treatment and avoid transplanting malignant cell back.**

5. Future Goals
The future of female fertility preservation comes to us by two different ways:

1. Groups who want to improve and optimize procedures and techniques used nowadays in clinic practices: ovarian tissue, oocyte and embryo cryopreservation.

2. Researches interested in looking for new strategies far from cryopreservation.

**Stem cells-based strategies (table) for ovarian regeneration and oocyte production has been proposed as future clinical therapies for female infertility.**

<table>
<thead>
<tr>
<th>Table: Characteristics of stem cells used in stem cell-based therapy research of infertility.</th>
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<tbody>
<tr>
<td><strong>ESCs</strong></td>
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<tr>
<td>Derived from inner cell mass of the blastocyst.</td>
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<tr>
<td><strong>Pluripotent</strong></td>
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<tr>
<td><strong>Prolonged proliferation.</strong></td>
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<tr>
<td><strong>Indefinite self-renewal potential.</strong></td>
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<td><strong>Immortal, cell lines remain intact for long periods of time.</strong></td>
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<td><strong>Ethical concerns.</strong></td>
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</table>

6. Conclusions

- The need for female fertility preservation is emerging because the incidence of cancer in young population is increasing and its treatment usually leads to infertility. Fertility preservation is also needed because many women prefer to postpone childbearing.

- Nowadays there are some options available in order to preserve female fertility, most common are: ovarian tissue, oocyte and embryo cryopreservation. These techniques consist in freezing the sample following different protocols according to their characteristics and storing them in LN2 for future applications.

- Not all procedures can be used for all patients: while ovarian tissue cryopreservation is more suitable for pre-puberal girls, oocyte and embryo cryopreservation is the main election for women at reproductive ages.

- Protocols about samples cryopreservation have been designed to prevent as much as possible cell alterations and death. Somatic cells for slow frozen oocytes are much lower than vitrified ones, that’s the reason why slow freezing oocytes has not been used anymore in clinics.

- Future goals on female fertility preservation are the improvements and optimization of current procedures.

- There are some researchers looking for new strategies, they believe that an ideal fertility preservation approach would prevent delays in coming year saving treatment and avoid transplanting malignant cell back. Stem cells strategies (in particular OSCs) may offer one route to achieve this goal.

7. References