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INFERTILITY

- Nearly 72.4 million people or 15% of couples experience fertility problems
- The etiology therein is caused by the female in 30% of cases and the male in another 30%. In 30% of cases, both the male and female contribute to the lack of pregnancy success, and unexplained infertility is observed in up to 10% of cases
- Couples who suffer from fertility issues and no respond to first line treatment(IO) often use assisted reproductive technologies (ART), such as intrauterine insemination (IUI), *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (3, 4). Since the first birth of an IVF baby in 1978, IVF has been the predominant treatment for female infertility (5). ICSI is an advanced ART wherein a single sperm is introduced into the oocyte through the zona pellucida via microinjection
- During the past two decades, modern infertility treatments as in vitro oocytes fertilization, egg donation, pregnancy surrogacy, heterologous artificial fertilization and preimplantation diagnosis (PGD),

INTRODUCTION

- Of particular interest are questions on how to improve IVF results in older women and solve infertility in women with premature ovarian failure (POF) or other types of ovarian infertility.
- In contrast to natural menopause, women diagnosed with POF may undergo unpredictable ovarian function leading to intermittent and unpredictable menses in 50% of cases, and conceive and deliver a child in ~5 to 10% of cases. In addition, other authors use the term primary ovarian insufficiency (POI) [3] instead of POF [4]. Most POF women, however, lack ovarian follicles and there are no practical evidences that their infertility can be solved by IVF, except for oocyte/embryo donation cycles

- At present, it is obvious that the IVF approach is subjected to the increased demands of older women. In developed world, “graying” of infertility populations and of infertility services was recently reported by Norbert Gleicher and colleagues as “an impeding revolution nobody is ready for” [7]. In this IVF series article authors reviewed this approach indicating that IVF live birth rates decrease to close to zero after 42 years, with no clinical pregnancies between 46–53 years.
- The ovarian reserve reflects the total of ovarian follicles including non-growing follicles (NGFs) together with those that are growing recruited in the preantral and antral stages phases that can finally reach ovulation. Women are born with a finite pool of ovarian follicles that decreases dramatically during intrauterine life from a peak of about 7 million to 1 million at birth. During childhood the descent continues, so that at the age of menarche about 400,000 persist follicles. Finally at menopause there are only less than 1,000 follicles in the ovaries
- Heide Schatten and colleagues [8] deal with a vital role of mitochondria in oocyte functions. Oocytes of women affected by metabolic disorders, such as diabetes or obesity and oocyte aging, can be improved by transfer of mitochondria from cells with mitochondrial integrity into mitochondria-impaired oocytes.

DOR

- According to these concepts, three different scenarios may occur: a normal decrease of ovarian reserve with age, a lower ovarian reserve set prenatally with an usual postnatal decay, or a decrease of ovarian reserve during adverse postnatal environmental or nutritional challenges (5). Anyhow, the diminished ovarian reserve (DOR) constitutes one of the most important therapeutic challenges in assisted reproduction, since the ovarian response to gonadotropin stimulation is an essential prognostic factor

- Pluripotent stem cells are able to differentiate into cells that arise from the 3 germ layers—ectoderm, endoderm, and mesoderm—from which all tissues and organs develop [10]. Commonly, stem cells are derived from two main sources: early embryos (embryonic stemcells (ESCs)) and adult tissue (adult stem cells).
- ESCs are pluripotent stem cells derived from the inner cell mass of the blastocyst . The essential characteristics of ESCs include derivation fromthe preimplantation embryo, prolonged proliferation in their pluripotent state, and stable developmental potential to form derivatives of all three embryonic germ layers
- Stem cells can also be derived from extraembryonic tissues (amnion, chorion, placenta, and umbilical cord)

- Mesenchymal stem cells (MSCs) are one of themost common adult, multipotent stem cells [12]. They can be derived from a variety of tissues including bone marrow, adipose tissue, bone,Wharton’s jelly, umbilical cord blood, and peripheral blood [13]. MSCs are adherent to cell culture dishes and are characterized by specific surface cell markers.
- MSCs are able to differentiate into mesoderm-derived tissue such as adipose tissue, bone, cartilage, and muscle [13– 16]. Recently, MSCs were differentiated into neuronal tissue which is derived from the ectoderm. This is an example of transdifferentiation, that is, when a cell from one germ layer (mesoderm) differentiates into neuronal tissue (ectoderm)

Stem Cell-Derived Oocytes: Current Knowledge and Future Perspectives

- Stem cell-based strategies for ovarian regeneration and oocyte production have been proposed as future clinical therapies for treating infertility in women.
- On the other hand, it has been suggested that infusion of human-derived stem cells could supply a fitting ovarian niche to maintain or promote follicular rescue in patients with impaired or aged ovarian reserves. Human studies propose bone marrowderived stem cells (BMDSC) both mesenchymal and hematopoietic are feasible candidates to promote ovarian rejuvenation

- In other words, we know that in increasing age, ovarian function cannot be maintained, despite the ovarian germ stem cell activity and several experimental studies indicated that ovarian function decline is mainly related to the aging of the ovarian germ cell nests but not to the aging of the ovarian germ stem cells (53, 54). All these concepts would serve as a basis to propose the improvement of the niche as a method for the rejuvenation of the ovary.

CURRENT APPLICABLE ASSISTED REPRODUCTIVE TECHNOLOGIES

- However, it is significantly more difficult to predict the transmission of mitochondrial DNA (mtDNA) mutations by PGD due to asymmetric segregation of mtDNA
- Mitochondrial replacement therapy (MRT) is a series of processes that involve extracting nuclear DNA with a small amount of cytoplasm from an oocyte or zygote in a patient with mutated mtDNA and then transplanting it into donor cytoplasm where the donor's nucleus has been removed, replacing it with non-mutated mtDNA from the donor (12). Currently, there is no cure for mitochondrial disease, and MRT is the only technology proposed to eliminate the risk of disease inheritance in offspring. Advanced female age is another important cause of infertility, partially due to a cytoplasmic deficiency which induces chromosomal abnormalities in aged oocytes resulting in the failure of fetal development. MRT can also be employed to resolve cytoplasmic defects due to aging

ASSISTED REPRODUCTIVE TECHNOLOGIES FOR THE FUTURE

- **Oocytes or sperm can be differentiated from pluripotent stem Cells**
- If oocytes and sperm could be made from adult somatic cells, they could be used for people who suffer from infertility or genetic diseases
- In the future, we anticipate being able to generate sperm or oocytes from PSCs for oocyte- or sperm-free patients (Fig. 2). Thus far, the main source of artificial germ cells is PSCs. Below, we introduce cell types, advantages, and disadvantages of PSCs

Table 1. Characteristics of stem cells in the treatment of infertility by stem cells

	ESCs	MSCs	SSCs	iPSCs
Source of generation	inner cell mass cells of blastocysts	cord blood, bone marrow, and adipose tissue	testicular tissues	human somatic cells
Self-renewal capacity	differentiate into derivatives of three major germ layers	mesodermal-derived tissue, such as bone, cartilage, adipose tissue, and muscle	differentiate into the derivatives of all three primary germ layers	differentiate into the derivatives of all three primary germ layers
Nature of cells	pluripotent	multipotent	pluripotent	pluripotent
Ethical concerns	Ethical and moral concerns present	No ethical or moral concerns	No ethical or moral concerns	No ethical concerns
Clinical applications	Restricted	Widely used	Widely used	Widely used
Immuno-rejection	Yes	No	Yes	Yes

ESCs: embryonic stem cells; MSCs: mesenchymal stem cells; SSCs: spermatogonial stem cells; iPSCs: induced pluripotent stem cell.

Intrauterine adhesion formation

- The etiology of intrauterine adhesions is believed to be due to fibrosis of the opposing uterine walls after destruction of the endometrial basalis layer.
- It is a catastrophic process whereby uncontrolled deposition of extracellular matrix (ECM) and fibrillar collagens occurs. The stromal compartment is replaced by fibrous tissue, and the glands are replaced by inactive cubo-columnar epithelium

Current treatment for Asherman syndrome

- Primary prevention of IUA is key since once the pathological cascade begins, the reversal becomes much more difficult. AAGL's guideline for primary prevention of IUA states: the application of an adhesion barrier following surgery that may lead to endometrial damage significantly reduces the development of IUAs in the short term, although limited fertility data are available following this intervention, grading the evidence as level A. The second guideline with level B evidence emphasizes the key point: that operative procedures that disrupt the endometrial basalis, especially postpartum, more likely contribute to IUA than those that resect intracavitary pathology, e.g., polypectomy and myomectomy of type 0 fibroids

- Treatment of IUA should be considered only for patients
- with AS, as the risk of treating asymptomatic IUA outweighs
- the benefit. Because of the risk of uterine perforation and false
- tract formation, blind cervical probing and uterine curettage is
- discouraged now with the advent of ultrasound and hysteroscopy