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Current Developments in Assisted Reproduction

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Infertility is a disease, defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse [1]. It is estimated that infertility affects 13% to 15% of couples worldwide [2]. Moreover, 20% of couples consult their general physician because of difficulty conceiving, and half of those couples (10%) require specialist care. In many cases, infertility can be effectively treated only by means of assisted reproductive techniques (ART), which comprises all fertility treatments in which oocytes, sperm and embryos are handled. Since the first successful application of *in vitro* fertilization in 1978, ART has become widely spread all around the world, and more than 3 million of *in vitro* conceived babies were born. While we celebrate the significant advances made in the field of ART, intensive search for innovative approaches aimed at increasing birth rates and at reducing the occurrence of complications associated to ART, mainly ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies is ongoing.

Ovarian stimulation is a key component of ART and is directed towards the ultimate goal of obtaining an adequate number of good quality oocytes while preventing excessive ovarian response. Recent years have witnessed a significant expansion of the pharmacological armamentarium useful in ovarian stimulation protocols. Introduction in clinical practice of recombinant gonadotropins (FHS, LH, and hCG) and GnRH antagonists are among the most remarkable in this respect. Corifollitropin alfa is a long acting FSH analogue, able to initiate and sustain multiple follicular growth for seven days. As remarkable advantage, corifollitropin alfa may allow the development of simplified treatment regimens with the increase in injection-free interval [3]. GnRH antagonists are used to prevent premature LH surges in women undergoing controlled ovarian hyperstimulation for ART programs. GnRH antagonists have been shown, in comparison to GnRH agonists, to reduce significantly the risk of OHSS [4]. This iatrogenic and potentially life threatening condition, resulting from excessive ovarian stimulation, is estimated to affect 1%-10% of ART cycles. GnRH antagonists also contribute to OHSS prevention by allowing to trigger ovulation with a bolus of a GnRH agonist as an alternative to hCG [5].

The selection of embryos with maximal developmental and implantation potential has relayed on morphological parameters and cleavage rate, as assessed by light microscopy. This methodology has many recognized pitfalls and shortcomings, as underlined by the failure of approximately 8 of 10 transferred embryos to implant. Novel technologies for non-invasive assessment of embryo viability in assisted reproduction are under evaluation. The so called omics, including genomic, transcriptomic, proteomic and metabolomic analysis strategies are among the more innovative and promising [6]. A factor possibly implicated in the relative low implantation rate is the elevated frequency of embryonic numerical chromosomal abnormalities. Preimplantation genetic screening (PGS) aims at identifying viable euploid embryos potentially having higher chances of producing a pregnancy. The main indications for PGS are advanced maternal age, repeated implantation failure, repeated miscarriage, and eventually severe male factor infertility. Unfortunately there is no evidence of a beneficial effect of PGS as currently applied of a beneficial effect of PGS, as currently applied, on ART outcome [7]. PGS clinical efficiency might benefit of emerging novel technologies, including single nucleotide polymorphism (SNP) and comparative genomic hybridization (CGH) allowing the simultaneous enumeration of all chromosomes [8].

Improvements in the field of cryobiology, with particular reference to the introduction of the vitrification technique, have made possible to efficiently preserve oocytes. Survival rates and clinical outcomes comparable to those obtained with fresh oocytes in ART programs have been recently reported [9]. Although oocyte cryopreservation is still considered experimental by major regulatory bodies in Europe and United States, the favorable perspectives offered by this technology in term of fertility preservation for reasons related to age, has led to the extension of clinical application of oocyte freezing also to non-medical indications. A debate regarding the potential social implications of this emerging indication was recently sparked [10].

Concerns regarding the human risk from ART have risen with the advent of intracytoplasmic sperm injection (ICSI). The invasiveness of this technique allowing the injection of the spermatozoon into the oocyte, and thus circumventing all the natural selective barriers, prioritizes the need for careful risk estimation. Although further monitoring is required to draw firm conclusions, recent outcome studies are partially reassuring. Only a slight increase in fetal chromosomal abnormalities and congenital malformations has been associated to ICSI [11]. It is important also to note that emerging data support the concept that ICSI-conceived boys are not at increased risk of altered reproductive health, as reflected by salivary testosterone concentrations measured in teenagers [12].

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