FVV in ObGyn, 2014, 6 (2): 77-80

Mini-Review

IVM results are comparable and may have advantages over standard IVF

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Abstract

Retrieval of immature oocytes from unstimulated ovaries, followed by in vitro maturation (IVM) was originally proposed in order to avoid side effects of gonadotropin administration. The target is to eliminate or significantly reduce the risk of ovarian hyperstimulation syndrome (OHSS) in patients with polycystic ovary syndrome (PCOS), drug cost and burden on patients. This technology was also suggested in treatment of normo-ovulatory women, fertility preservation or infrequent conditions such as failure of oocytes to mature or repeated development of poor quality embryos. In this study we intended to examine the possibility that IVM results may be comparable to standard IVF. A PubMed database search from 1999-2013 was carried out for publications concerning the indications of IVM and study the possibility that IVM results may be comparable to standard IVF.
In vitro maturation of the oocytes procedures obtained up to 35% clinical pregnancy rate in young women, comparable with in vitro fertilization (IVF) in many programs. The obstetric and perinatal outcomes of IVM cycles are comparable with IVF/ICSI cycles.
In conclusion IVM may gradually replace IVF in certain cases, as the technique continues to develop and pregnancy rates continue to increase, being a promising and simple alternative approach to standard IVF in various indications.

Key words: **ART, ART outcomes, In Vitro Maturation, IVM, oocytes, pregnancy rate, pregnancy outcome.**

Introduction

IVM was initially introduced by Pincus and Enzmann (1935), using immature rabbit oocytes capable of undergoing spontaneous maturation and fertilization in vitro. Cha et al. (1991) were the first to succeed with IVM in humans. The first group that succeeded in producing a child via IVM were Trounson et al. (1994), using oocytes recovered from an untreated ovary in patients with polycystic ovaries. In-vitro maturation (IVM) has advanced significantly from its initial description to its current widespread clinical applications. Despite these advances, however, there are still many controversial issues surrounding this treatment. Given that IVM is an emerging protocol (at least in humans), there are many controversial areas of debate, and especially regarding the subject of the best candidates for IVM; how should we select our patients?

We have conducted a review of the literature in the PubMed database from 1999-2013 for publications concerning the indications of IVM and examined the possibility that IVM results may be comparable to standard IVF. Taking into consideration that no standard protocol exists up to present in different centres, all forms of IVF (unstimulated, stimulated, oestrogen suppressed) are considered together.

Results

Several studies covered different indications for IVM: Patients with normo-ovulatory cycles (Dal Canto et al., 2006; Fadini et al., 2009; Mikkelsen et al., 1999, 2001), polycystic ovarian syndrome (PCOS) or normo- ovulatory women with polycystic ovaries (PCO) (Child et al., 2001, 2002; Soderstrom-Anttila et al., 2005), fertility preservation (Huang et

al., 2010; Maman et al., 2011; Shalom-Paz et al., 2010), poor ovarian response (IVM may serve the last choice of treatment after the failure to achieve pregnancy in traditional IVF) (Liu et al., 2003) and in rare conditions such as rescue of oocytes which have failed to mature in stimulated cycles (Tan and Child, 2002) or cases with unexplained primarily poor quality embryos (Hourvitz et al., 2010).

Normo-ovulatory women may be treated with IVM. Since early studies, (Child et al., 2001; Mikkelsen et al., 1999, 2000, 2001; Soderstrom-Anttila et al., 2005) in which a 4%-25% clinical pregnancy rates were reported, there has been a constant improvement in results in normo-ovulatory patients of up to 30% pregnancy rate (Fadini et al., 2009, 2011). Del Canto et al. (2006) as well suggested that IVM was a good treatment with a comparable pregnancy rate to IVF, mainly due to the Italian law, which allows a maximum of three oocytes per IVF cycle and prohibits embryo or zygote (2PN cells) cryopreservation. IVM oocytes fertilize and undergo development in vitro with rates similar to in vivo matured control oocytes. In IVM cycles implantation and pregnancy rates are lower compared with controlled ovarian stimulation treatments, but accurate patient selection can improve IVM clinical outcome (Fadini et al., 2013). The main advantages of the IVM protocol in normo-ovulatory patients are: elimination of the side-effects of drug stimulation and reduction of the costs of the entire procedure, both in terms of time consumption and patient costs for drugs.

PCOS patients are prone to develop ovarian hyperstimulation syndrome (OHSS) with conventional IVF treatments. A potentially useful alternative for women with PCOS is earlier retrieval of immature oocytes from small antral follicles, without using hormonal stimulation, followed by IVM of those oocytes. Substituting IVM in PCOS patients eliminates the risk of OHSS and lowers the cost of treatment. From early 2000 until the present, studies have demonstrated a encouraging pregnancy and delivery rate in PCOS patients undergoing IVM treatments of 21.9%-29.9% (Child et al., 2001, 2002; Ellenbogen et al., 2011; Soderstrom-Anttila et al., 2005). Recent publications report up to 32%-44% pregnancy and 22-29% delivery rates (Shalom-Paz et al., 2011, 2012), comparable with IVF pregnancy rates results of 38%-45% (Shalom-Paz et al., 2012). In another study of Junk and Yeap (2012) the transfer of a single blastocyst embryo obtained after IVM in patients with PCOS was proposed. They obtained a live birth rate of 42.4% per oocyte collection and 45.2% per embryo transfer. In 20 oestrogen suppressed in vitro maturation cycles the implantation, pregnancy and delivery rates were 17.5%, 40% and 40% respectively (Vitek et al., 2013). Indeed SART lists higher clinical pregnancy rate for young women as > 46% in 2012. However in Europe the pregnancy and delivery rates in this group of patients undergoing ICSI was 35.5% and 24.3% respectively (Ferraretti et al., 2013). de Ziegler et al. (2012) opposed the need of IVM in the GnRH antagonist era. However, his results didn't take into consideration the fact that with GnRH-agonist used as a trigger to control the risk of ovarian hyperstimulation syndrome, higher pregnancy losses were observed (Humaidan et al., 2005). On the other hand, the dual trigger approach (GnRH-agonist + lowhCG) revealed 2.9% of OHSS complications (Griffin et al., 2012). Even applying the strategy of ovarian stimulation using the combination of GnRH antagonist with GnRH agonist to trigger ovulation and freezing all of the oocytes or embryos for later use (Devroey et al., 2011) do not eradicated OHSS totally as severe OHSS after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol was described (Fatemi et al., 2014).

The emerging technology of IVM in oocyte retrieval has recently become another option for fertility preservation. This procedure can be done without hormonal stimulation and within a short time frame; oocytes being collected during the follicular phase, within up to 13 days from cancer diagnosis and the resulting embryos either vitrified or fertilized and cryopreserved (Huang et al., 2010; Shalom-Paz et al., 2010). To shorten the period of time until cancer treatment, studies by Maman et al. (2011) reported luteal phase treatment with a reasonable number of harvested oocytes. Therefore, in cases of cancer patients, especially in which hormonal treatment is contraindicated and those who must start chemotherapy without delay, IVM might be the only option to preserve fertility. However, up to now, no data are available concerning pregnancy rates in this group of patients.

One flow of IVM had been suggested, as mature eggs at retrieval often give rise to embryos that result in live birth pointing that they are not "really" IVM oocytes. However, from 1224 oocytes retrieved in IVM cycles only 15.6% were found mature up to six hours after retrieval vs. 64.9% that matured in vitro after 6-48 hours (Ellenbogen et al., 2011). No differences were found regarding fertilization and cleavage rates or top quality embryos developed from either oocytes (Ellenbogen et al., 2011).

There are concerns about possible undesirable effects on babies conceived after IVM. However, Soderstorm-Anttila et al. (2006) showed comparable

complications and malformations for babies born after undergoing IVM and IVF. Buckett et al. (2007) described a normal pregnancy course for IVM patients compared to IVF cycles. Fadini et al. (2012) reported normal growth and development of 196 babies born from IVM cycles. Recently, Chian and Cao (2014) reported 1421 healthy infants born following immature oocyte retrieval and IVM.

IVM as part of ART is not free of possible unknown future complications. It is known that epigenetic modifications may alter normal development of the embryo. Those changes are established during oocyte growth, and IVM may modify the normal maturation of the oocytes (Bao et al., 2000). Moreover, the mature oocyte is responsible for reprogramming the male chromatin after fertilization. This ability is dependent on oocyte maturation (Gioia et al., 2005). It is unknown if this process may be affected by IVM. In vitro maturation may have deleterious effects on the organization of the meiotic spindle and chromosome alignment of human oocytes. This finding may be a possible explanation for the reduced developmental potential of oocytes matured in vitro compared with those matured in vivo (Li et al., 2006). However despite the great achievements obtained in treating infertile couples by standard IVF during the last 34 years, it has become evident in recent years that ovarian stimulation, although a central component of IVF, may itself have detrimental effects on oogenesis, with production of aneuploidity (Baart et al., 2007), reduced embryo quality, lower endometrial receptivity and perhaps also perinatal outcomes (Santos et al., 2010).

Conclusion

In vitro maturation of oocytes is a simple procedure. It is an economical and less stressful procedure for women. Puncture is simple and safe and it can improve the disrupted endocrine environment and induce a spontaneous recovery of ovulation and pregnancy in women with PCOS without other infertile factors. It can avoid short-term complications, such as ovarian hyperstimulation syndrome and possible long-term complications, such as hormone dependent neoplasm's including breast and ovarian cancers. Studies to date have not identified an alarming rate of congenital anomalies in IVM children, and studies which have followed up children to the age of 2 years old have provided reassuring results regarding their growth and development.

IVM holds great promise as an alternative to assisted reproductive technologies and may be the procedure of choice not only for infertile patients but also for obtaining oocytes for donation or fertility preservation. Improving embryonic-endometrial synchrony through pharmaceutical or other manipulation of endometrial/uterine receptivity will hopefully result in future improvements in IVM success rates.

Proper counselling of these patients about advantages and disadvantages of the procedure should be performed routinely.

The goal of the ART is to help patients fulfil their most basic desires of reproduction and continuity, using technology that was only imaginary not long ago. These techniques are not yet flawless and may be associated with taking some calculated risks and courageous decision making, without which we would never have been able to help so many people and create so many happy families.

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