Development of in vitro maturation techniques for clinical applications

Zhi-Yong Yang, M.D.[a] and Ri-Cheng Chian, Ph.D.[a,b]

[a] Center for Reproductive Medicine, Tenth People's Hospital of Tongji University, Shanghai, People's Republic of China; and
[b] Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada

In vitro maturation (IVM) refers to maturation in culture of immature oocytes at different stages that may or may not have been exposed to short courses of gonadotropins. The source of immature oocytes is an important feature for subsequent embryonic development, pregnancy, and healthy live births. IVM is an effective treatment that has already achieved significant outcomes of acceptable pregnancy and implantation rates and has led to the births of several thousand healthy babies. As the development of IVM treatment continues, an attractive possibility for improving the already successful outcome is to combine a natural-cycle in vitro fertilization (IVF) treatment with immature-oocyte retrieval followed by IVM of those immature oocytes. If the treatment processes can be simplified for immature-oocyte retrieval, different types of infertile women may be able to take advantage of these treatments. Mild-stimulation IVF combined with IVM treatment may represent a viable alternative to the standard treatment. Although IVM treatment is still considered to be experimental, it is now time to reconsider the IVM technology and its development. Mild-stimulation IVF combined with IVM may prove to be not just alternatives to standard treatments, but potentially first-line treatment choices. (Fertil Steril® 2017;108:577–84. ©2017 by American Society for Reproductive Medicine.)

Key Words: IVM, oocyte, immature, IVF, mild stimulation

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/19103-24447

Initial attempts of human in vitro fertilization (IVF) in the 1930s used in vitro matured (IVM) oocytes (1–4) because it was impossible to obtain human in vivo matured oocytes. The landmark work on IVM of human immature oocytes was carried out in the 1960s (5, 6), and human IVF techniques were also established with the use of IVM oocytes (7–10). Therefore, one can assume that current advanced assisted reproductive technologies (ART) for infertility treatment are based on the development work of IVM.

In the 1970s, laparoscopy was introduced to collect human mature oocytes from preovulatory follicles (11), resulting in the possibility to retrieve in vivo matured oocytes for IVF (12). Although the first human live birth resulting from IVF was produced with the use of natural-cycle IVF (13), this procedure was gradually replaced by controlled ovarian hyperstimulation combined with IVF treatment because the number of oocytes retrieved determined the embryos available for transfer, which in turn directly affected the chance of successful pregnancy (14–16).

At the beginning, clomiphene citrate (CC) was used as a single ovarian stimulation agent (17–19). Subsequently, in combination with hMG, it was used to generate multiple follicle developments and to increase the yield to more than one oocyte (20–22). However, current standard protocols use gonadotropins (recombinant or hMG) combined with LHRH agonists to prevent the problem of premature ovulation with the aim of obtaining an average of 10–15 mature oocytes per retrieval. Although high-dose gonadotropin treatments may obtain more oocytes, this approach is associated with a number of adverse short- and long-term side-effects, including a greater risk of ovarian hyperstimulation syndrome (OHSS) (23). Thus, natural-cycle and mild-stimulation IVF as well as IVM treatments have become appealing options to infertile couples.

Today, given the efficiency of IVF and improvements in the culture system, natural-cycle IVF or mild stimulation may be more suitable for women undergoing IVF treatment. Several studies have shown that natural-cycle IVF treatment has advantages over standard-stimulation IVF treatment, particularly in the management of women with low ovarian reserve (24, 25). In contrast to standard-stimulation IVF treatment, the aim of mild stimulation is to develop safer and patient-friendlier protocols where the risks of the treatment are minimized. Interestingly, despite theoretic advantages, mild IVF treatment has not become a mainstream approach in the United States. A recent large retrospective study found a significant decrease in live birth rate associated with increasing FSH dose regardless of the number of oocytes

Received June 2, 2017; accepted August 1, 2017.
Z.-Y.Y. has nothing to disclose. R.-C.C has nothing to disclose.
Reprint requests: Ri-Cheng Chian, Ph.D., Department of Obstetrics and Gynecology, McGill University, Montreal, Canada (E-mail: ri-cheng.chian@mcgill.ca).

Fertility and Sterility® Vol. 108, No. 4, October 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.08.020

retrieved (26), cautioning against high doses of FSH in IVF treatment cycles, albeit falling short of recommending mild IVF treatment. There is also evidence that mild stimulation or modified natural cycle protocols may have equal or even improved success rates compared with conventional IVF in women with a history of poor ovarian response (27).

Recovery of immature oocytes followed by IVM is a potentially useful treatment for infertile women. This method seems particularly effective for women with polycystic ovaries (PCO) or polycystic ovarian syndrome (PCOS)–related infertility, because there are numerous antral follicles within the ovaries of this group of patients (28–30). To date, IVM treatment has been mainly applied to women with PCOS and is not regarded to be applicable to all types of infertility with acceptable outcomes (31). It is clear that IVM treatment is not likely to replace the current stream of IVF treatments. In 2013, the Practice Committees of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology indicated that IVM should be performed only as an experimental procedure evaluating both efficacy and safety in carefully selected patients (32).

As we accumulate more experience and outcome data, natural-cycle IVF, mild-stimulation IVF, and IVM treatment may prove to be not just alternatives to standard stimulation treatments, but potentially first-line treatment choices (33). In the development of IVM treatment, one very attractive possibility for enhancing successful outcomes is to combine natural-cycle IVF treatment with immature egg retrieval followed by IVM of those immature oocytes (34). It has been proven that the use of IVM technology can thus be broadened to treat women suffering from all types of infertility with acceptable pregnancy and live birth rates (35–38). The aim of the present review is to share our views of the development of IVM technology.

DEFINITION OF IN VITRO MATURATION

The oocyte is a unique cell in a woman's body, owing to its special structure, function, and undergoing meiosis. Meiotic progression in the oocyte is defined as the oocyte maturation from reinitiation of the first meiotic division to the metaphase II (MII) stage accompanied by cytoplasmic maturation to successfully prepare the oocyte for fertilization and early embryonic development (39). In vivo meiotic resumption in the oocyte is initiated in response to the preovulatory surge of LH. The LH surge triggers oocyte maturation from the germinal vesicle (GV) stage to MII. For infertility treatment with the use of IVF technology, the patients are given hCG to induce the completion of oocyte meiosis in the follicles to retrieve mature MII oocytes 36 hours after hCG injection. Without hCG injection in IVF treatments, most of the retrieved oocytes would be at an immature GV stage.

Human immature GV-stage oocytes can be matured spontaneously to MII in vitro when they are removed from the antral follicles and cultured in the proper culture media. This is the biologic definition of oocyte IVM. IVM of human immature oocytes has developed as a clinical procedure a few decades after the first live birth from IVM oocytes (40). However, the techniques used for IVM of human immature oocytes differ in protocols, and the clinical definition of IVM treatment also differs from the biologic definition of oocyte IVM. Such differences include the source of immature oocytes that may not be at the GV stage owing to patient selections and different stimulation protocols. In some cases, the human immature oocytes were retrieved from follicles that have been stimulated for a few days with the use of gonadotropins to support moderate follicle growth and triggered with the use of hCG before oocyte retrieval. A recently proposed clinical definition of IVM is based on the size of follicles during the immature oocyte retrieval (41), but that proposed definition may be cumbersome and complicated. It has been criticized that a definition based on the size of follicles is not scientifically justified, and such a definition can lead to false results in interpreting the follow-up of children conceived with the use of IVM techniques (42, 43).

It is interesting to mention here that the first reports of pregnancies from IVM oocytes were from stimulated cycles where the retrieval of immature oocytes was followed by IVM and IVF (44, 45), in which the IVM procedure of immature oocytes was not based on the size of follicles. It seems to be difficult to clearly define the clinical meiotic status of oocytes, because there are different situations with patient selections and the sources. Therefore, the definition of clinical IVM should be defined according to the origin of immature oocytes to clarify for follow-up the outcomes derived from different sources of immature oocytes. Nevertheless, we think that clinical IVM treatment should be defined as IVM of any immature oocytes regardless of stage, from GV and MI to MII, for clinical application, because it involves the procedure of IVM for immature oocytes. It is important to point out for scientists, especially for basic scientists, that they should distinctly understand that the situation of clinical procedures is quite different from the laboratory procedures. It is not possible to evaluate the clinical procedures by evaluation of laboratory procedures for IVM of oocytes. The accumulation of our combined knowledge is to better understand the purpose of performing clinical IVM of oocytes and to use this knowledge for our health care.

SOURCE OF IMMATURE OOCYTES FOR IVM

As mentioned above, today's human IVF technology was developed with the use of IVM oocytes derived from surgical materials (8). Thus far, there is no exclusive IVM technology applied in the world (30). Since the first report of a pregnancy in a woman with anovulatory PCOS after undergoing IVM and IVF (46), several groups have made efforts to develop this treatment for infertile women with PCO or PCOS, because a large number of antral follicles in the ovaries are seen in infertile women with PCO or PCOS. This group of patients is sensitive to ovarian stimulation with the use of gonadotropins and has an increased risk of OHSS compared with women who have normal ovaries. The technique involves modified IVM treatment, with priming with the use of FSH or hCG before immature oocyte retrieval. It seems that the successful pregnancy rates with the use of IVM treatment correlated with the number of immature oocytes retrieved (47).