Assisted reproductive technology (ART) has helped several million women overcome childlessness due to infertility. Initial attempts in 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 at that time. The landmark work on IVM of human immature oocytes was carried out in 1960s [5, 6]; the human IVF techniques were also established with IVM oocytes [7–10]. Therefore, we can say all current advanced ART for infertility treatment is based on the early development work of IVM.

In the 1970s, laparoscopy was introduced to collect human mature oocytes from preovulatory follicles [11], resulting in the first reported case of in vivo matured oocytes in IVF [12]. Although the first human live birth resulting from IVF was produced by natural cycle IVF [13], this procedure was gradually replaced by 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]. Initially, clomiphene citrate (CC) was used as a single ovarian stimulation agent [17–19]. Subsequently, it was utilized in combination with human menopausal gonadotropin (HMG) to generate multiple follicle developments and to increase the yield of more than one oocyte [20–22]. To prevent the problem of premature ovulation, gonadotropins (recombinant or HMG) were combined with pituitary downregulation with LHRH agonists (referred at the time as controlled ovarian hyperstimulation or COH, but now called conventional IVF) with the aim of obtaining an average of 10–15 mature oocytes per retrieval from each woman.

In recent years, however, the protocols for ovarian stimulation with IVF treatment have undergone considerable changes, especially following the introduction of LHRH antagonists, which block LH for a few days within the woman’s natural cycle and permit milder forms of stimulation (mild IVF) with the aim of reducing complications and focusing on the quality rather than quantity of the oocytes.

Although high-dose gonadotropin COH cycles are associated with more oocytes collected, this approach is associated with a number of adverse short-and long-term side effects, including greater risks of ovarian hyperstimulation syndrome (OHSS) [23]; pulmonary embolus; maternal, fetal, and neonatal complications, such as preterm labor, preterm delivery, and low birthweight babies (both premature and SGA); and lastly, greater inconvenience and
increased cost. Thus, mild and natural cycle IVF, as well as IVM treatment, has become appealing options to more and more 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. Natural cycle, without any gonadotropin stimulation, is encumbered by a number of problems, including an increased risk of failure to retrieve oocytes and an absence of embryo available for transfer. Nevertheless, there has been a resurgence of interest in natural cycle IVF treatment in recent years because the efficiency of IVF technology has improved markedly [24–26], including modifications, such as the addition of GnRH antagonist and FSH add-back (modified natural IVF). With these adjustments, premature ovulation is no longer a problem. Several studies have shown that natural cycle IVF treatment has advantages over conventional COH IVF treatment with downregulation, particularly in the management of women with low ovarian reserve [27, 28].

In contrast to conventional IVF treatment, the aim of mild stimulation is to develop safer and more patient-friendly protocols where the risks of the treatment are minimized. Mild stimulation is defined as administration of low-dose exogenous gonadotropins, and/or for a shorter duration in GnRH antagonist co-treated cycles, or when oral compounds (CC, aromatase inhibitors) are used for ovarian stimulation, with the aim of retrieving fewer than eight oocytes [29, 30]. Mild stimulation using CC in combination with low doses of gonadotropins can also be considered a realistic option for good prognosis patients undergoing IVF [31].

Interestingly, despite theoretical advantages, mild IVF treatment has not become a mainstream treatment approach in the USA at the present time. Although mild ovarian stimulation is an appropriate option to consider for certain patient groups or based on patient preference [32], current evidence pointing to fewer cryopreserved embryos and lower success rates per cycle could be regarded as potential disadvantages and limit its acceptability for patients [33]. A recent large retrospective study found a significant decrease in live birth rate associated with increasing FSH dose regardless of the number of oocytes retrieved [34], 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 [35].

Recovery of immature oocytes followed by IVM of these oocytes is a potentially useful treatment for women with infertility. This method is 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 [36–38]. Apart from women with PCOS, IVM treatment may be also offered to women who are delayed responders or who are over responding during stimulation in IVF cycles as an alternative to cancelation with acceptable pregnancy and live birth rates [39, 40]. To date, IVM treatment has been mainly applied to women with PCOS and is not regarded as applicable to all types of infertility. However, there is a growing number of women requiring IVF treatment
where ovarian stimulation is either rejected by the women due to concerns about side effects or contraindicated, such as in women with a previously treated estrogen-dependent cancer.

As the development of IVM treatment continues, one very attractive possibility for enhancing the successful outcome is combining natural cycle IVF treatment with immature egg retrieval followed by IVM of those immature oocytes [41]. It has been proven that the use of IVM technology can thus be broadened to treat women suffering from all causes of infertility with acceptable pregnancy and live birth rates [42–45].

More recently, Paulson et al. [46] postulated that one of the barriers to access to fertility care is the relative complexity of fertility treatments. If these treatment processes can be simplified, more infertile women may be able to take advantage of the treatments. A more simplified, milder IVF treatment approach represents a viable alternative to standard treatment. As we accumulate more experience and outcome data, mild stimulation IVF and IVM may prove to be not just alternatives to standard treatments, but potentially first-line treatment choices. All these exciting new treatment options are explored in depth in this book. The aim of this book is to share our experience and protocols with the ART fraternity.

Part I covers the scientific rationale for follicular development by outlining ovarian endocrinology and how somatic cells interact with oocytes during follicular development: the mechanism of oocyte maturation, and how these have led to understand the current concept and protocols for oocyte maturation in vivo and in vitro. Also discussed is the importance of mitochondrial changes during oocyte growth and maturation. Here, we emphasize that follicular maturation (or growth) and oocyte maturation are two totally different concepts. Follicular maturation (or growth) refers to the relatively lengthy process developing over several weeks from primordial follicle to preovulatory follicle; oocyte maturation is triggered by LH surge in vivo and refers to the maturation from the fully grown oocyte from germinal vesicle (GV) stage to metaphase-II (M-II) stage, in order to receive sperm for fertilization. Oocyte maturation can occur spontaneously in vitro after releasing from follicles with suitable culture conditions.

Part II covers the differences between natural cycle IVF treatment and stimulated IVF cycles and the different hormone profiles from follicular fluid in natural cycle IVF treatment. It also covers the standard ovarian stimulation protocols and their outcome in general, including cumulative success rates with natural cycle IVF treatment. Also discussed are how to prevent and manage ovarian hyperstimulation syndrome (OHSS) and which patients are suitable for natural cycle IVF treatment.

Part III covers mild stimulated IVF treatments both with exogenous gonadotropins and aromatase inhibitors. It also covers mild stimulation protocols for fertility preservation in women at risk of infertility following cancer treatment. An alternative treatment, INVO procedure, is described, and accessible infertility care and genetic aspect of recurrent implantation failure are also discussed.

Finally, Part IV covers IVM as clinical treatment for women with PCOS and how to avoid the severe OHSS with IVM treatment. It also covers the
methodology of immature oocyte retrieval and all laboratory and clinical aspects of IVM treatment. Also discussed are obstetrical and congenital outcomes of IVM babies and how the development of IVM treatment may be applied to all types of infertile women with natural cycle IVF combined with IVM treatment.

We wish to express our gratitude to all of the authors for their diligence and patience and for generously sharing their knowledge and expertise. We are also very grateful to Ms. Martine Chevry, who provided considerable editorial expertise and kept the project on track.

Montreal, QC, Canada  
Ri-Cheng Chian, MSc, PhD

London, UK  
Geeta Nargund, FRCOG

Stanford, CA, USA  
Jack Y.J. Huang, MD, PhD

References

Development of In Vitro Maturation for Human Oocytes
Natural and Mild Approaches to Clinical Infertility
Treatment
Chian, R.-C.; Nargund, G.; Huang, J.Y.J. (Eds.)
2017, XVII, 376 p. 67 illus., 56 illus. in color., Hardcover
ISBN: 978-3-319-53452-7