Chapter 15
Implementing and Managing Natural and Modified Natural IVF Cycles

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Introduction

The story of the birth of the first IVF baby on 25th July 1978 is well known to all reproductive medicine specialists. It was achieved in a natural cycle for a woman with tubal factor infertility. As means of controlling the Luteinizing Hormone (LH) surge were not available at that time, Patrick Steptoe and Robert Edwards turned to the advantages of a physiological cycle to overcome the problems of an early surge which is associated with stimulated cycles [1].

Nearly four decades after Louise Brown was born, it is now estimated that approximately five million babies have been born worldwide by IVF [2]. Following the advent of Gonadotrophin Releasing Hormone (GnRH) agonist downregulation in the early 1980s protocols were developed where following high Follicular Stimulating Hormone (FSH) stimulation multiple oocytes could be collected for fertilisation with a view to improving the selection potential of embryos [3]. However, iatrogenic complications, high cost of fertility treatment, concerns regarding supraphysiological hormonal levels on both mothers and embryos have led clinicians to rethink their established views on cycle management to seek more physiological approaches to stimulation. This was aided by the development of GnRH antagonists, introduced to the market for the first time in 2001, where patients could be treated within their own natural cycle and milder and more natural protocols could be developed [3]. As a

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result a global trend has emerged over the last few years favouring milder and more natural approaches to ovarian stimulation. The efficiency of these approaches has also been enabled by advances in ultrasound such as Doppler and 3D and by innovative technology in the laboratory such as in vitro maturation (IVM).

In 2006 an international society for implementing mild and natural approaches to stimulation (ISMAAR) was established. Its members advocate that these approaches in IVF treatment are as effective as conventional IVF in achieving comparable pregnancy rates. At the same time they are more patient friendly, resulting in fewer short and long term side effects promoting more natural and physiological conceptions that result in healthier babies [4].

Physiology of Selection of a Dominant Oocyte

In the female, the cells (*oogonia*) that will give rise to the oocytes released during menstrual cycles are formed during foetal life. The oogonia increase rapidly in number and some differentiate into the so-called *primary oocytes* until about the 5th month of foetal life after which some cell degeneration takes place. At birth a female carries 700,000 to 2,000,000 primary oocytes. Cell death or *atresia* continues and at puberty there are only around 400,000 primary oocytes of which fewer than 500 will be ovulated [5, 6].

As oocytes cannot be produced after birth, oocytes released later in life derive from cells that could have been dormant for more than 40 years.

A primary oocyte together with its surrounding flat epithelial cells is known as a *primordial follicle*. Around 1000 primordial follicles start growing every month. Complete follicular development takes over 220 days and can be classified into three phases according to the developmental stage and follicular gonadotrophin dependence. First, the initial recruitment of resting primordial follicles, second the development of pre-antral and early antral follicles and finally cyclic recruitment of a limited cohort of antral follicles followed by the selection of a single dominant follicle during the mid-follicular phase of the menstrual cycle [7, 8].

The very early stages of follicular development, which are also known as "initial recruitment", are possibly under the control of intra-ovarian autocrine and paracrine factors and they are independent of FSH and LH [9]. However, the selection of a dominant follicle from a cohort of antral follicles, also known as "cyclic recruitment", is dependent on FSH [8].

FSH levels increase in the late luteal phase up to the onset of menstruation and the early follicular phase of the following cycle. This inter-cycle rise is also named the "*FSH window*" and stimulates "cyclic recruitment". A cohort of 4–6 healthy follicles start accumulating FSH in their follicular fluid and in the follicle destined to become dominant, this FSH concentrates at a critical threshold [10, 11]. In that follicle FSH stimulates production of estradiol in excess of the production in the non-dominant follicles. Its development becomes a self-supported event through a negative feedback loop where the oestrogen secreted by the dominant follicle suppresses the release of FSH to such levels that the remaining follicles which do not contain adequate numbers of FSH receptors or

have not reached a certain stage of maturity (narrowing of FSH window) cannot aromatise androgens to estrogens at a sufficient rate and develop an androgenised environment. It is only the follicles with an estrogenic environment that are rescued for further growth, while those with an androgenic environment become atretic. The above shows that the duration of the FSH window as well as its magnitude is important. The selected dominant follicle continues to grow despite low FSH values. This is partially explained by an increase in the sensitivity of the dominant follicle to FSH. In the midfollicular phase and onwards the follicle becomes dependent on LH.

One needs to realise that in older women or those with low ovarian reserve, high stimulation with FSH will only affect the small number of follicles that are undergoing cyclic recruitment and will not affect follicles undergoing early recruitment. Therefore, in these circumstances downregulation protocols may be counterproductive. In such women natural or modified natural IVF appears to be a more logical treatment.

Definitions

In the nearly four decades since the birth of the first IVF baby several protocols have been developed with nomenclatures often creating a confusion in terminology both among clinicians and among patients.

ISMAAR has published a clarification of the terminology used for ovarian stimulation protocols (The ISMAAR proposal on terminology for ovarian stimulation in IVF, Table 15.1) [12].

Natural Cycle IVF

This refers to IVF performed during a patient's spontaneous cycle without the use of any stimulation medication or medication to trigger final oocyte maturation. The cycle develops spontaneously and oocyte retrieval is timed according to the patient's LH surge. The aim of this treatment is to harvest a naturally selected oocyte at the lowest possible cost.

Table 15.1 ISMAAR definitions (www.ismaar.org)

Terminology	Aim	Methodology
Natural cycle IVF	Single oocyte	No medication
Modified natural cycle IVF	Single oocyte	hCG only antagonist and FSH/hMG add-back
Mild IVF	2–7 Oocytes	Low dose FSH/hMG, oral compounds and antagonist
Conventional IVF	≥8 Oocytes	Agonist or antagonist conventional FSH/hMG dose

Natural cycle IVF usually has higher cancellation rates due to spontaneous ovulation but is valuable in specific circumstances, such as when increased oestradiol levels are to be avoided or because of patient preference for a drug free IVF cycle. The patients should be counselled about cancellation rates. The cycle is monitored with serial ultrasound scans and one or two hormone assays during the cycle. The timing of oocyte collection may be based on an optimum level of serum estradiol (E2) and LH and/or ultrasound measurement of follicular diameter and endometrial thickness [13, 14]. Tests may be carried out to detect urinary LH surge prior to oocyte collection. Follicular flushing may be used during ultrasound-directed follicle aspiration. IVF and embryo transfer techniques are similar to those used in stimulated cycles. Luteal support is not used unless specifically indicated.

No specific protocol template can be applied and both the frequency of monitoring and the timing of the oocyte retrieval are dependent on the woman's cycle.

Modified Natural Cycle IVF

This term should be applied when IVF is being performed during a spontaneous cycle with the use of exogenous hormones or any drugs aiming to collect a naturally selected single oocyte but with a reduction in the chance of cycle cancellation. The drugs used may include:

1. The use of human chorionic gonadotrophin (hCG) to induce final oocyte maturation with or without subsequent luteal support.
2. The administration of GnRH antagonist to block the spontaneous LH surge with or without FSH or human menopausal gonadotrophin (hMG) as add-back therapy.

Luteal support is usually administered.

Standardised template protocols in this type of treatment can include the following:

- *Natural cycles with hCG and indomethacin only*: Monitoring in these cycles is performed via serial ultrasound scans and measurements of serum E2 and LH. The first scan may be performed between day 8–9 of the cycle or as early as day 5 depending on the woman's natural cycle pattern. HCG is used to induce final oocyte maturation when a follicle is ≥16 mm. Indomethacin tablets 50 mg three times a day are administered from the day of the trigger or earlier if there is a spontaneous rise in LH or a spontaneous surge, in order to inhibit ovulation [15].
- *Natural controlled cycles*: Monitoring in these cycles is again performed via serial ultrasound scans and measurements of serum E2 and LH. The first scan can be performed as early as day 5 of the cycle. A GnRH antagonist is administered together with add back FSH (max dose 150 IU) once the leading follicle is 13–14 mm. HCG is used to induce final oocyte maturation when a follicle is >17 mm. Luteal support is administered.

Potential Advantages of a Natural or Natural Based IVF Cycle

As mentioned earlier in the introduction, the recently noted global trend toward natural and milder stimulation approaches to IVF treatment can be attributed to emerging evidence associating certain advantages to these types of treatment. Some of these advantages are summarised below:

- The natural selection process of the dominant follicle is maintained. This ensures recruitment and development of only the best quality follicles and oocytes in each menstrual cycle, a classic example of quality versus quantity.

The importance of preserving the element of natural selection is associated with the development of better quality gametes, especially in cases of women of advanced age with diminished reserve. In 2001 Wikland et al. compared antagonist protocols with a low starting FSH dose (150 IU) and a high FSH dose (225 IU) and showed that whilst there was a difference in the number of oocytes retrieved in the high dose group, both groups have comparable results in pregnancy rates [16]. Similar results were presented by Yong et al. in a randomised trial comparing cycle outcomes with starting doses of 150 IU r-FSH versus 225 IU [17]. They concluded that higher doses of stimulation could not compensate for the well documented age related decline in numbers of follicles available for stimulation. In conclusion, aiming to develop higher numbers of oocytes does not ensure a better outcome.

- The natural based protocols involve the use of either no stimulation or low dose drugs for a short period of time, hence minimising any potential long-term side effects.

It is evident that increasingly more women are delaying childbirth, which leads to an increase in the numbers of those who are seeking fertility treatment. As a result the fertility drugs are among the fastest growing group of drugs and it is therefore understandable that they will be attracting studies on potential long-term side effects. Periodically there are epidemiological studies linking fertility drugs to an increased incidence of various cancers. Evidence is already available on the prolonged use of clomiphene citrate for ovulation induction. Use of clomiphene citrate for 12 consecutive months or more has linked this drug to the development of borderline ovarian tumours. The evidence is less clear when it comes to the gonadotrophins used in stimulation and whilst some studies have implicated their use with an increased risk of ovarian cancer, others have failed to show such a relationship [18]. There is similarly conflicting evidence when it comes to any associations between fertility drugs and development of breast cancer but there are studies that have shown an increased risk between use of clomiphene citrate and endometrial cancer [19]. When interpreting the currently available results, we must bear in mind that the fertility drugs were first used in the 1960's and that longer term follow up may reveal new evidence. These limitations are evident to both clinicians and patients seeking milder forms of treatment.

- The risk of ovarian hyper-stimulation syndrome (OHSS) is either eliminated or decreased significantly.

OHSS is an iatrogenic complication that can be very challenging for clinicians and distressing for patients. The prevalence of moderate to severe OHSS in literature varies between 1 % and 10 % [20]. It makes sense that the risk of developing OHSS drops significantly with lower doses of stimulation and that it is completely eliminated in natural cycles and nearly eliminated in modified natural cycles [21].

- The use of no or less drugs decreases the cost of the individual cycle.

When directly comparing the cost of individual cycles, natural and natural modified cycles are cheaper due to the use of no or decreased amounts of drugs [13].

- The discomfort and emotional burden experienced by patients is considered to be less in mild stimulation approaches [22].

The overall discomfort experienced by patients was not higher than that experienced in conventional IVF cycles despite the higher number of IVF cycles undertaken with the mild approach. The cycle drop-out rates were nearly halved in mild stimulation compared to those with standard treatment [22].

- The endometrium maintains its physiological properties.

Embryo implantation is an extremely well controlled process at both cellular and hormonal levels. Therefore, maintaining a receptive endometrium is of paramount importance. There is recent evidence suggesting that conventional IVF protocols using GnRH-agonist may alter the receptivity properties of the endometrium [23]. Horcajadas and his colleagues concluded that endometrial development after a GnRH antagonist mimics the natural endometrium more closely than after a GnRH agonist at both morphological and molecular levels [23]. They showed that no changes were seen in morphology and at the molecular level only 23 genes were dysregulated when high doses of drugs were used. Similar results have been shown earlier by Mirkin and co-workers but they concluded that although ovarian stimulation causes structural and functional changes compared with natural cycles, small changes were found when gene expression patterns were compared, and that ovarian stimulation may therefore not have a major impact on endometrial receptivity [24]. The clinical implications of this need to be evaluated further.

- Lower and more physiological doses of stimulation can result in better quality embryos.

Baart et al. conducted a study where they randomly allocated mild stimulation and conventional stimulation protocols to two groups of patients [4]. One hundred and eleven patients were included in the study, all under the age of 38. The mild stimulation protocol involved stimulation with 150 IU of rFSH commenced on day 5 and the conventional stimulation protocol involved down-regulation with a GnRH agonist and stimulation with 225 IU. A day 3 embryo biopsy was conducted. The study was terminated prematurely after an interim analysis showed lower embryo aneuploidy results in the mild stimulation group. They concluded that reducing the interference with ovarian physiology results in a sufficient number of chromosomally normal embryos [4].

- The success rates of natural cycles are comparable to those of stimulated IVF.

Early studies on natural cycle IVF have reported live birth rates between 3.8 and 18.8 % per cycle [25]. The lower pregnancy rate per started cycle in natural and modified natural-cycle IVF compared with conventional IVF stimulation is a logical consequence, since only one follicle is available in natural and modified natural IVF cycles. The higher cost effectiveness of stimulated cycles when compared to natural cycles has been the argument that established stimulated IVF as the predominant form of assisted reproduction treatment. Ultimately, a higher number of retrieved oocytes is expected to result in higher pregnancy rates through an improved embryo selection potential compensating for any inefficiencies in the embryology lab.

Four randomised controlled trials (RCT's) conducted between 1991 and 2004 that compared natural cycles with hCG only to clomid stimulated cycles, hMG and GnRH analogue long protocol cycles and flare stimulation cycles with FSH and GnRH analogues all demonstrated lower success rates for natural cycles [26–29].

In contrast a study conducted by Nargund et al. in 2001 showed that the overall cost effectiveness of natural cycle IVF may be higher compared to conventional IVF if natural cycles are offered in a series of consecutive cycles [13]. They felt that the lower cost per cycle, the lower stress levels observed during treatment and the ability to have "back to back" treatment in successive cycles made natural cycle IVF a viable option for many women. In their study they looked at 52 women who underwent a total of 181 cycles. The median age of the study group was 34 with a range 24–40. They included women with both primary and secondary infertility and tubal damage and women with primary infertility and poor ovarian reserve. They calculated the cost of natural cycles based on use of hCG and indomethacin including three scans per cycle. They concluded that after four cycles the cumulative probability of pregnancy was 46 % with a live birth rate of 32 % [13, 30].

The concept of offering a series of natural cycles also attracted Pelinck et al. who conducted a large cohort study in 2006 and looked into the cumulative pregnancy rate after three modified natural IVF cycles in good prognosis patients [31]. A total of 844 treatment cycles in 350 patients of 36 years of age with no previous IVF treatment were included. The ongoing pregnancy rate was 8.3 % with one cycle and 20.8 % after up to three cycles of treatment. A year later Pelink et al. showed that cumulative pregnancy rates reached 44.4 % after nine modified natural cycles [32].

- Performance of transvaginal retrieval under local anaesthetic.

Since the great majority of natural cycles involve harvesting of only one follicle, the idea of performing the oocyte retrieval under local anaesthetic can be very appealing to both patients and clinicians. The patient avoids exposure to sedation medication, the procedure time and time for recovery in the unit is shortened and the cost of treatment decreases. Selection of patients following assessment of access to the dominant follicle and patient suitability in terms of pain expectations and anxiety levels is important.

- The laboratory procedures are less time consuming due to the low number of oocytes utilised.
  This contributes to a lower cost of the cycles [33].
- Decreased multiple pregnancy rates.

Clearly multiple pregnancies are the result of the embryo transfer policy and not of ovarian stimulation in itself. The argument for more aggressive stimulation and increased oocyte yield has been the need for an increased number of embryos. In natural cycles single embryo transfer (SET) becomes the default as there is rarely more than one embryo available, there is less embryo wastage and the process appears more efficient.

Challenges and Solutions

Natural cycles require closer monitoring and can be associated with lack of efficacy and overall high cancellation rates (28.9 %) [14]. The high cancellation rates are due to unfavourable cycle events that impact on outcome and occur more frequently than in conventional superovulation IVF cycles. These unfavourable cycle events are inadequate growth of the dominant follicle, premature surge in LH, spontaneous ovulation before oocyte retrieval, failure to collect an oocyte and fertilisation failure or no transferable embryo.

- Use of an antagonist.

The use of an antagonist in the so-called natural modified cycle has decreased the incidence of premature ovulation from 16.6 % seen in natural cycles to 4.2 %. To avoid follicular developmental arrest, concomitant substitution with rFSH is thought necessary [33]. In natural modified cycles 81 % of started cycles reach oocyte retrieval and 36.5 % reach embryo transfer (or 61.1 % of successful retrievals) as shown by a large cohort study conducted by Pelinck et al. in 2007 [32].

- Use of indomethacin.

The administration of FSH, albeit for a short period and at low doses, could be considered as an inconvenience for some. The use of indomethacin can be an alternative. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) and has been shown to effectively delay ovulation [15, 34–36]. It inhibits the production of prostaglandins which are essential for follicle rupture and ovulation. Indomethacin administered before ovulation prevents follicle rupture without apparent effects on menstrual cycle length or FSH, LH, oestradiol and progesterone concentrations [37, 38].

- Use of Clomiphene.

The continuous use of Clomiphene as another alternative for suppressing the premature LH surge has been described by Teramoto and Kato in a large scale retrospective study [39]. They have successfully used a protocol where clomiphene was used from day 3 of the cycle and continued until the day before triggering oocyte maturation and 83 % of the cycles studied reached oocyte retrieval.

- Use of advanced ultrasound and Doppler images to assess the quality of the developing follicle and optimise the timing of HCG administration for oocyte maturation.

Management of natural IVF cycles requires greater judgement and knowledge of physiological processes. This has led to a greater variability in the success rates and contributed to the initial trend of decreased prevalence of these cycles. The use of colour flow Doppler to assess the perifollicular blood flow can provide additional information about the quality of the developing follicle and contribute to optimising the timing of oocyte retrieval.

Nargund et al. conducted a study assessing the perifollicular flow of stimulated follicles on the day of the trigger injection and immediately before follicular aspiration for oocyte retrieval [40]. They demonstrated a significant relationship between follicular peak systolic velocity (PSV), the ability to recover an oocyte and the subsequent production of morphologically normal embryos. They demonstrated that 72 % of the follicles with PSV ≥10 cm/s produced grade 1 or grade 2 preimplantation embryos. Their findings were consistent with previous studies on PSV and pulsatility index (PI) in unstimulated ovaries, at the times of follicular rupture at ovulation, that had demonstrated a rise in the PVS associated with the preovulatory rise in LH [41]. The authors acknowledge the difficulties in accurately assessing the flow velocity in small vessels and the importance of the operator's skills in obtaining accurate findings.

- Use of a series of treatment cycles to improve efficiency.

As shown by Nargund et al. after four cycles the cumulative probability of pregnancy can reach 46 % with a live birth rate of 32 % [13].

Indications

The advantages of natural cycle IVF that we analysed earlier give rise to some of the indications for this type of treatment.

1. Medical contraindications to the use of stimulation drugs and the development of high levels of estradiol.

   Patients with conditions that can be adversely affected by high levels of estradiol, such as hypercoagulable diseases, history of oestrogen dependent carcinomas, etc., can opt to have natural based IVF. In the case of cancer patients awaiting cancer treatment, one should obviously consider the time frame available for IVF treatment and determine whether serial natural cycles or a single mild short stimulation protocol with or without the use of anti-estrogens would be preferable.
2. Women with a history of severe OHSS or those at significant risk of developing severe OHSS.

This group of women can find stimulation very stressful and are challenging to treat. No or low doses of drugs for a short period of time eliminates or decreases the risk of OHSS.

3. IVM cycles.

IVM cycles were initially indicated to eliminate the risk of OHSS in patients with polycystic ovaries.

The increased interest in natural cycle IVF has subsequently led to the evaluation of natural cycle IVM. As we described earlier in a natural cycle, normally only a single follicle develops to the pre-ovulatory stage and ovulates its mature oocyte. Many small follicles also grow in the ovaries during the same follicular phase of the menstrual cycle. These will eventually become atretic following the selection of the dominant follicle but there is a narrow window when they can still be retrieved. Immature oocytes retrieved at this stage have been successfully matured in vitro and fertilised, and they have resulted in several pregnancies and healthy live births [42].

Prevention of ovulation from the dominant follicle in a natural IVM cycle remains important. HCG can be administered 36 h before oocyte retrieval when the size of the leading follicle has reached 12–14 mm in diameter and before atresia takes place in the non-dominant follicles and still result in retrieval of metaphase 2 (MII) oocytes from the majority of leading follicles. It is therefore possible to combine natural cycle IVF with IVM as an alternative to natural cycle IVF, and clinical pregnancy rates of 35 % have been achieved for a selected group of women with various causes of infertility without recourse to ovarian stimulation [42].

Natural IVF with IVM, where in vivo matured oocytes are collected with immature IVM oocytes in the same unstimulated cycles could become a standard approach in assisted reproductive technology (ART) treatments. Lim et al. showed promising results in a study conducted in 2009 that revealed a 40.4 % clinical pregnancy rate from such a combined natural IVF/IVM approach [43].

The applications of IVM have been extended to other groups of patients, such as poor responders and cancer patients. Poor responders to previous gonadotrophin stimulation were found to benefit from immature oocyte collection in an unstimulated natural cycle. In 2001 Child et al. showed that in a group of women with poor ovarian response the number of embryos produced and available for embryo transfer was similar to that for previous IVF treatments [44]. Some of the applications of IVM cycles may be limited by the technical difficulties of oocyte retrieval from follicles less than 7 mm in size.

4. Poor responders and women with poor ovarian reserve.

This group of patients remains difficult to treat and different ovarian stimulation protocols have been tried without a single protocol appearing superior to the other. Natural cycle IVF has been shown to be equally effective as a "*Flare*" protocol with a GnRH agonist in younger poor responders [29]. It has also been shown to produce results comparable to conventional IVF in patients aged between 37 and 43 years old with low ovarian reserve [45]. Natural cycle IVF in poor responders resulted in a higher number of cycles scheduled for oocyte

retrieval and thus a higher pregnancy rate per started cycle compared to conventional IVF, where cycles have a higher cancellation rate [46]. Better embryo quality, better endometrium receptivity and the possibility of repeating the cycle monthly can account for the better results seen in this group of patients.

5. Older patients with or without previous poor response to stimulation.

   For these patients who, as a rule, are expected to have a diminished ovarian reserve, the benefits of a natural cycle appear clear. Natural selection of the dominant follicle improves embryo quality. By applying the knowledge we derived from studies on poor responders, the combination of an expected poor response and decreased oocyte quality can justify the use of these protocols as first line treatment in this group of patients [47]. Contrary to these results, Tomasevic et al. in 2007 concluded that age related poor responders rarely benefit from natural IVF cycles [48].

6. Male factor only

   Relatively high pregnancy rates have been reported in young couples with severe male factor infertility as the only fertility-compromising factor. In this category of patients, the success rate per started cycle was 13.3 % and cumulative pregnancy rates of 43.8 % after six successive cycles have been reported [49, 50]. These can be seen as encouraging results that justify offering this type of treatment to such couples while keeping treatment side effects to a minimum. Contrary to these findings Pelinck et al. concluded that natural and modified natural cycles may not be the best choice of treatment protocols in male factor infertility due to the lower fertilisation rate that consequently results in fewer embryo transfers per started cycle [14].

7. Patient preference.

   There is an increased tendency among patients to seek more physiological approaches to fertility treatment. This is understandable considering the possible advantages attributed to these cycles. The simplicity and short duration, the lack or low doses of medication and the fact that natural IVF cycles can fit into patients' spontaneous menstrual cycles are some of the reasons that make these cycles appealing to patients [51, 52].

Conclusions

Natural cycle IVF set the cornerstone upon which ART developed. Conventional IVF once thought as a sophisticated treatment method has been associated with complications such as OHSS, thrombosis, increased multiple pregnancy rates, high treatment cost and increased patient symptomatology including anxiety.

There is now sufficient evidence showing that natural and modified natural IVF cycles are more patient friendly with low complication rates and can be performed at lower cost. Treatment can be given in back to back cycles and there is evidence of similar success rates to conventional IVF treatment in older women and those with low ovarian reserve. Natural cycle IVF is more successful in centres with ultra-

sound expertise especially in ovarian and uterine Doppler. Natural and Modified natural cycle IVF is valuable in specific circumstances and especially when combined with IVM it will play an increasing role in the treatment options that should be available to couples.

References

1. Edwards RG. IVF, IVM, natural cycle IVF, minimal stimulation IVF-time for a rethink. Reprod BioMed Online. 2007;15(1):106–19.
2. ESHRE ART fact sheet. http://www.eshre.eu/Guidelines-and-Legal/ART-fact-sheet.aspx.
3. Heyden C. GnRH analogues: applications in assisted reproductive techniques. Eur J Endocrinol. 2008;159:S17–25.
4. Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, Macklon NS, Fauser BC. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. Hum Reprod. 2007;22:980–8.
5. Sadler TW. Gametogenesis. In: Langman's medical embryology. 6th ed. North Carolina, USA; 1990. p. 3–14. Published by Williams & Wilkins.
6. Sadler TW. Ovulation to implantation. In: Langman's medical embryology. 6th ed. North Carolina, USA; 1990. p. 21–38. Published by Williams & Wilkins.
7. Gougeon A. Regulation of ovarian follicular development in primates: facts and hypotheses. Endocr Rev. 1996;17:121–55.
8. McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. Endocr Rev. 2000;21:200–14.
9. Fortune JE, Cushman RA, Wahl CM, Kito S. The primordial to primary follicle transition. Mol Cell Endocrinol. 2000;163:53–60.
10. McNatty KP, Hunter WM, MacNeilly AS, Sawers RS. Changes in the concentration of pituitary and steroid hormones in the follicular fluid of human graafian follicles throughout the menstrual cycle. J Endocrinol. 1975;64(3):555–71.
11. Brown JB. Pituitary control of ovarian function—concepts derived from gonadotrophin therapy. Aust N Z J Obstet Gynaecol. 1978;18:46–54.
12. Nargund G, Fauser BCJM, Macklon NS, Ombelet W, Nygren K, Frydman R. The ISMAAR proposal on terminology for ovarian stimulation for IVF. Hum Reprod. 2007;22(11):2801–4.
13. Nargund G, Waterstone J, Bland JM, Philips Z, Parsons J, Campbell S. Cumulative conception and live birth rates in natural (unstimulated) IVF cycles. Hum Reprod. 2001;16(2):259–62.
14. Pelinck MJ, Hoek A, Simons AHM, Heineman MJ. Efficacy of natural cycle IVF: a review of the literature. Hum Reprod Update. 2002;8(2):129–39.
15. Nargund G, Wei C. Successful planned delay of ovulation for one week with indomethacin. J Assist Reprod Genet. 1996;13(8):683–4.
16. Wikland M, Bergh C, Borg K, Hillensjo T, Howles CM, Knutsson A, Nilsson L, Wood M. A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI. Hum Reprod. 2001;16:1676–81.
17. Yong PY, Brett S, Baird DT, Thong KJ. A prospective randomized clinical trial comparing 150 IU and 225 IU of recombinant follicle-stimulating hormone (Gonal-F) in a fixed-dose regimen for controlled ovarian stimulation in in vitro fertilization treatment. Fertil Steril. 2003;79:308–15.
18. Brinton LA, Lamb EJ, Moghissi KS, et al. Ovarian cancer risk associated with varying causes of infertility. Fertil Steril. 2004;82:405–14.
19. Brinton LA. Long-term effects of ovulation-stimulating drugs on cancer risk. Reprod BioMed Online. 2007;15(1):38–44.

20. Serour GI, Rhodes C, Sattar MA, Aboulghar MA, Mansour R. Complications of assisted reproductive techniques: a review. Assist Reprod. 1999;9(4):214–32.
21. Fauser BC, Nargund G, Nyboe Andersen A, Norman R, Tarlatzis B, Boivin J, Ledger W. Mild ovarian stimulation for IVF: 10 years later. Hum Reprod. 2010;25(11):2678–84.
22. Heijnen EMEW, Eijkemans MJC, De Klerk C, Polinder S, Beckers NGM, Klinkert ER, Macklon NS, Fauser BCJM. A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority study. Lancet. 2007;369:1–8.
23. Martinez-Conejero JF, Simon C, Pellicer A, Horcajadas JA. Is ovarian stimulation detrimental to the endometrium? Reprod BioMed Online. 2007;15(1):45–50.
24. Mirkin S, Nikas G, Hsiu JG, Diaz J, Oehninger S. Gene expression profiles and structural/functional features of the peri-implantation endometrium in natural and gonadotropin-stimulated cycles. J Clin Endocrinol Metabol. 2004;89:5742–52.
25. Daya S, Gunby J, Hughes EG, Collins JA, Sagle MA, YoungLai EV. Natural cycles for in-vitro fertilisation: cost effectiveness analysis and factors influencing outcome. Hum Reprod. 1995;10:1719–24.
26. MacDougall MJ, Tan SL, Hall V, Balen A, Mason BA, Jacobs HS. Comparison of natural with clomiphene citrate-stimulated cycles in in vitro fertilization: a prospective, randomized trial. Fertil Steril. 1994;61:1052–7.
27. Ingerslev HJ, Hojgaard A, Hindkjaer J, Kesmodel U. A randomized study comparing IVF in the unstimulated cycle with IVF following clomiphene citrate. Hum Reprod. 2001;16:696–702.
28. Levy MJ, Gindoff P, Hall J, Stillman RJ. The efficacy of natural versus stimulated cycle IVF-ET. Fertil Steril. 1991;56 Suppl 1:S15.
29. Morgia F, Sbracia M, Schimberni M, Giallonardo A, Piscitelli C, Giannini P, Aragona C. A controlled trial of natural cycle versus microdose gonadotropin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization. Fertil Steril. 2004;81:1542–7.
30. Verberg MFG, Macklon NS, Nargund G, Frydman R, Devroey P, Broekmans FJ, Fauser BC. Mild ovarian stimulation for IVF. Hum Reprod Update. 2009;15(1):13–29.
31. Pelinck MJ, Vogel NE, Hoek A, Simons AH, Arts EG, Mochtar MH, Beemsterboer S, Hondelink MN, Heineman MJ. Cumulative pregnancy rates after three cycles of minimal stimulation IVF and results according to subfertility diagnosis: a multicentre cohort study. Hum Reprod. 2006;21:2375–83.
32. Pelinck MJ, Vogel NE, Arts EG, Simons AH, Heineman MJ, Hoek A. Cumulative pregnancy rates after a maximum of nine cycles of modified natural cycle IVF and analysis of patient drop-out: a cohort study. Hum Reprod. 2007;22:2463–70.
33. Pelinck MJ, Vogel NE, Hoek A, Arts EG, Simons AH, Heineman MJ. Minimal stimulation IVF with late follicular phase administration of the GnRH antagonist cetrorelix and concomitant substitution with recombinant FSH: a pilot study. Hum Reprod. 2005;20(3):642–8.
34. Okuda Y, Okamura H, Kanzaki H, Fujii S, Takenaka A, Wallach EE. An ultrastructural study of ovarian perifollicular capillaries in the indomethacin-treated rabbit. Fertil Steril. 1983;39:85–92.
35. Kadoch I, Al-Khaduri M, Phillips S, Lapense L, Couturier B, Hemmings R, Bissonnette F. Spontaneous ovulation rate before oocyte retrieval in modified natural cycle IVF with and without indomethacin. Reprod BioMed Online. 2008;16:245–9.
36. Kawachiya S, Matsumoto T, Bodri D, Kato K, Takehara Y, Kato O. Short-term, low-dose, non-steroidal anti-inflammatory drug application diminishes premature ovulation in natural-cycle IVF. Reprod BioMed Online. 2012;24:308–13.
37. Athanasiou S, Bourne TH, Khalid A, Okokon EV, Crayford TJ, Hagstrom HG, Campbell S, Collins WP. Effects of indomethacin on follicular structure, vascularity, and function over the peri-ovulatory period in women. Fertil Steril. 1996;65:556–60.
38. Hester K, Harper MJK, Duffy D. Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam blocks ovulation in non-human primates when administered to simulate emergency contraception. Hum Reprod. 2010;25:360–7.
39. Teramoto S, Kato O. Minimal ovarian stimulation with clomiphene citrate: a large-scale retrospective study. Reprod BioMed Online. 2007;15:134–48.
40. Nargund G, Bourne T, Doyle P, Parsons J, Cheng W, Campbell S, Collins W. Association between US indices of follicular blood flow, oocyte recovery and preimplantation embryo quality. Hum Reprod. 1996;11(1):109–13.

41. Campbell S, Bourne TH, Waterstone J, Reynolds KM, Crayford TJ, Jurkovic D, Okokon EV, Collins WP. Transvaginal color blood flow imaging of the periovulatory follicle. Fertil Steril. 1993;60(3):433–8.
42. Lim JH, Yang SH, Chian RC. New alternative to infertility treatment for women without ovarian stimulation. Reprod BioMed Online. 2007;14:547–9.
43. Lim JH, Yang SH, Xu Y, Yoon SH, Chian RC. Selection of patients for natural cycle in vitro fertilization combined with in vitro maturation of immature oocytes. Fertil Steril. 2009;91(4):1050–5.
44. Child TJ, Abdul-Jalil AK, Gulekli B, Tan SL. In vitro maturation and fertilization of oocytes from unstimulated normal ovaries, polycystic ovaries, and women with polycystic ovary syndrome. Fertil Steril. 2001;76(5):936–42.
45. Papaleo E, De Santis L, Fusi F, Doldi N, Brigante C, Marelli G, Persico P, Cino I, Ferrari A. Natural cycle as first approach in aged patients with elevated follicle-stimulating hormone undergoing intracytoplasmic sperm injection: a pilot study. Gynaecol Endocrinol. 2006;22:351–4.
46. Bassil S, Godin PA, Donnez J. Outcome of IVF through natural cycles in poor responders. Hum Reprod. 1999;14:1262–5.
47. Ubaldi FM, Rienzi L, Ferrero S, Baroni E, Sapienza F, Cobellis L, Greco E. Management of poor responders in IVF. Reprod BioMed Online. 2004;10(2):235–46.
48. Tomasevic T, Korosec S, Virant Klun I, Drobnic S, Verdenik I. Age, oestradiol and blastocysts can predict success in natural cycle IVF-embryo transfer. Reprod BioMed Online. 2007;15(2):220–6.
49. Zhioua F, Zhioua A, Chaker A, M'solly S, Meriah S. Efficacy of intracytoplasmic sperm injection in a natural cycle with GnRH antagonists. Hum Reprod. 2004;49 Suppl 1:i105.
50. Vogel NEA, Pelinck MJ, Arts EG, Hoek A, Simons AH, Heineman MJ. Effectiveness of the modified natural cycle ICSI: results of a pilot study. Fertil Steril. 2003;80 Suppl 3:123.
51. Verberg MF, Eijkemans MJ, Heijnen EM, Broekmans FJ, de Klerk C, Fauser BC, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. Hum Reprod. 2008;23(9):2050–5.
52. Pistorius EN, Adang EM, Stalmeier PF, Braat DD, Kremer JA. Prospective patient and physician preferences for stimulation or no stimulation in IVF. Hum Fertil. 2006;9(4):209–16.