Commentary

# New alternative to infertility treatment for women without ovarian stimulation

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## Abstract

Natural cycle IVF produced the world first successful live birth, but slowly this treatment has been replaced by ovarian stimulated cycle IVF, because it has been believed ovarian stimulated cycle IVF will increase the number of available embryos for transfer. Therefore, it directly increases the chance of pregnancy from the treatment cycle. However, ovarian stimulation is always associated with side effects. The recovery of immature oocytes followed by in-vitro maturation (IVM) and IVF is an attractive alternative to stimulated cycle IVF. IVM treatment provides a successful option to infertile women with polycystic ovaries and polycystic ovary syndrome. It is now possible to combine natural cycle IVF with IVM as an alternative for a selected group of women with various causes of infertility without recourse to ovarian stimulation.

***Keywords:*** *IVM, live birth, natural cycle IVF, ovarian simulation, polycystic ovary syndrome*

Pincus and Enzmann (1935) attempted to mature mammalian oocytes *in vitro*. The initial in-vitro maturation (IVM) of human oocytes was reported almost 70 years ago (Pincus and Saunders, 1939), and they claimed that immature human oocytes can be matured following culture *in vitro* for approximately 12 h. This was corrected by Edwards (1965a,b) that immature human oocytes require 37 h of culture *in vitro* for maturation. This discovery permitted in-vitro matured human oocytes available to be fertilized *in vitro* (Edwards *et al*., 1969), and resulted in the world's first baby born from IVF, using in-vivo matured oocytes, almost a decade later (Steptoe and Edwards, 1978).

The first live birth following IVF of human oocytes was produced from a natural cycle IVF (Steptoe and Edwards, 1978). This was slowly replaced by ovarian stimulation IVF, because it is believed that the number of retrieved oocytes relates to the embryos available for transfer, and that this directly affects the probability of successful pregnancy (Lopata *et al*., 1978; Johnston *et al*., 1981; Jones *et al*., 1982). With current IVF treatment, women are usually pretreated for approximately 2 or 3 weeks with gonadotrophin-releasing hormone (GnRH)-agonist or GnRH-antagonist in combination with gonadotrophins to induce the development of multiple follicles in their ovaries. However, ovarian stimulation with these hormones is accompanied with side effects. Some women are extremely sensitive to stimulation with gonadotrophins and are at increased risk of developing ovarian hyperstimulation syndrome (OHSS) (Beerendonk *et al*., 1998). Severe OHSS is associated with occasional severe complications, while the long-term side effects of repeated hormone stimulation are unknown (Duckitt and Templeton, 1998; Brinton *et al*., 2005).

Women who have infertility due to anovulation in association with the polycystic ovary syndrome (PCOS) can be treated successfully without ovarian stimulation by immature oocyte retrieval followed by IVM, because there are numerous antral follicles within the ovaries in this group of patients (Cha and Chian, 1998). It has been found that the time course of human oocyte maturation *in vitro* is dependent on whether or not the patient is primed with human chorionic gonadotrophin (HCG) before immature oocyte retrieval (Chian *et al*., 1999, 2000). This observation has been confirmed by several reports (Nagle *et al*., 2002; Son *et al*., 2002, 2006; Lin *et al*., 2003). In comparison with stimulated cycle IVF, the major advantages of IVM treatment include avoidance of the risk of OHSS, reduced cost, and simplified treatment. So far, IVM treatment has been mainly applied to infertile women who have had polycystic ovaries visualized with an ultrasound scan.

Recently, there is an increasing interest in natural cycle IVF, primarily because it is more comfortable and has less side effects. This is even though there is the risk of failure in oocyte collection and consequently no embryo being available for transfer as a consequence (Lenton and Woodward, 1993; Daya *et al*., 1995). However, life-table analysis to calculate cumulative success rates after successive cycles of treatment has indicated that the cumulative probability of pregnancy is 46% with an associated live birth rate of 32% after four cycles of treatment (Janssens *et al*., 2000; Nargund *et al*., 2001). Moreover, the implantation and live birth rates per started cycle seem almost similar to one ovarian stimulated cycle, when compared with a natural cycle with intracytoplasmic sperm injection (ICSI) (Lukassen *et al*., 2003). Therefore, it is important to consider the best option for patients: undergoing two or three natural cycle IVF treatments or one ovarian stimulated cycle, when both methods achieve similar pregnancy and live birth rates within the same time span. In addition, natural cycle IVF or IVM may be the first choice for infertility treatment in countries such as Italy, where there is a maximum of three oocytes per IVF cycle that can be inseminated (Dal Canto *et al*., 2006).



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Throughout the reproductive life of the woman, cohorts of oocytes are removed from the non-growing pool and commence growth. During the follicular phase of menstrual cycle, usually only a single follicle grows to preovulatory stage and releases one oocyte for potential fertilization. It was reported that approximately 20 small antral follicles are selected and continued through to the preovulatory stages of development during each menstrual cycle (Hillier, 1994). Recently, it has been documented that there are two or three waves of ovarian follicular development in women during each menstrual cycle based on daily transvaginal ultrasonography, challenging the traditional theory of a single cohort of antral follicles that grow only during the follicular phase of the menstrual cycle (Baerwald *et al.*, 2003a,b).

Interestingly, it seems that atresia does not occur in the non-dominant follicles even after the dominant follicle is selected during folliculogenesis, because immature oocytes retrieved from non-dominant follicles have been successfully matured *in vitro* and fertilized and have resulted in several pregnancies and healthy live births (Paulson *et al.*, 1994; Thornton *et al.*, 1998). Therefore, one very attractive possibility for enhancement of the success of natural cycle IVF treatment is its combination with immature oocyte retrieval and IVM of those oocytes. If the mature oocyte from the dominant follicle were collected together with immature oocytes from the small follicles and matured and fertilized to produce several viable embryos, the chances of a pregnancy would be greatly increased.

It is important to prevent ovulation from the dominant follicle, due to the natural LH surge, when women are treated with natural cycle IVF combined with IVM. A pilot study has indicated that the best time to give 10,000 IU HCG is when the size of the dominant follicle reaches 12–14 mm in diameter and oocyte retrieval can be performed 36 h later (Lim *et al.*, 2007). Most oocytes collected from dominant follicles are at metaphase-II stage. Surprisingly, mature oocytes can sometimes be collected from the relatively small follicles.

The results are reported for a new approach to infertility treatment for 82 women with normal ovaries and regular menstrual cycles. The patients were less than 40 years of age (mean = 35.9 years) and had at least 2 years of infertility. The treatment was initiated from a baseline ultrasound scan on day 3 of menstrual cycle to ensure that there were more than seven small antral follicles presented in both ovaries. The second transvaginal ultrasound scan was repeated on day 8 of menstrual cycle. When a leading follicle reached 12–14 mm in diameter, 10,000 IU of HCG was administrated 36 h before retrieval. The collected mature oocytes were inseminated by ICSI and the immature oocytes were cultured in IVM medium supplemented with final concentrations of 75 mIU/ml of FSH and LH for 24 or 48 h (Chian *et al.*, 2004). The in-vitro matured oocytes were also inseminated by ICSI, and the resulting embryos were pooled together and then transferred 3 or 4 days later.

The results are shown in **Table 1**. The mature (1.2) and immature (6.8) oocytes were collected at oocyte retrieval. On average, 2.5 embryos were transferred to each patient. In all, 29 women became pregnant and the pregnancy rate per transfer was 35.4%. These results provide evidence that mature oocytes can be retrieved when the leading follicles reach 12–14 mm in diameter followed by HCG administration.

**Table 1.** Results of mature and immature oocyte retrieval and in-vitro maturation and fertilization, followed by embryo transfer in women with normal ovaries and regular menstrual cycles.

| *Variable* | *Value* |
|---|---|
| No. of patients | 82 |
| Age (years) | 35.9 ± 2.6 |
| *Mature oocytes retrieved* | |
| Total number | 99 |
| Mean | 1.2 ± 0.6 |
| *Immature oocytes retrieved* | |
| Total number | 619 |
| Mean | 6.8 ± 0.4 |
| No. of oocytes matured *in vitro* (%) | 495 (80) |
| No. of oocytes fertilized (%) | 371 (75) |
| No. of embryos cleaved (%) | 356 (96) |
| *Embryos transferred* | |
| Total number | 205 |
| Mean | 2.5 ± 0.5 |
| No. of clinical pregnancies (%) | 29 (35) |
| No. of implantation (%) | 39 (19) |

Values are mean ± standard deviation unless otherwise stated.

In conclusion, the results imply that selected women with various types of infertility can be treated efficiently by this new approach without ovarian stimulation, namely natural cycle IVF and IVM. This new treatment without ovarian stimulation will benefit many infertile women.

## References


Baerwald AR, Adams GP, Pierson RA 2003a A new model for ovarian follicular development during the human menstrual cycle. *Fertility and Sterility* **80**, 116–122.

Baerwald AR, Adams GP, Pierson RA 2003b Characterization of ovarian follicular wave dynamics in women. *Biology of Reproduction* **69**, 1023–1031.

Beerendonk CCM, van Dop PA, Braat DDM *et al.* 1998 Ovarian hyperstimulation syndrome: facts and fallacies. *Obstetrical and Gynecological Survey* **53**, 439–449.

Brinton LA, Moghissi KS, Scoccia B *et al.* 2005 Ovulation induction and cancer risk. *Fertility and Sterility* **83**, 261–271.

Cha KY, Chian RC 1998 Maturation *in vitro* of immature human oocytes for clinical use. *Human Reproduction Update* **4**, 103–120.

Chian RC, Lim JH, Tan SL 2004 State of the art in in-vitro oocyte maturation. *Current Opinion in Obstetrics and Gynecology* **16**, 211–219.

Chian RC, Buckett WM, Tulandi T *et al.* 2000 Prospective randomized study of human chorionic gonadotrophin priming before immature oocyte retrieval from unstimulated women with polycystic ovarian syndrome. *Human Reproduction* **15**, 165–170.

Chian RC, Gulekli B, Buckett WM *et al.* 1999 Priming with human chorionic gonadotropin before retrieval of immature oocytes in women with infertility due to the polycystic ovary syndrome. *The New England Journal of Medicine* **341**, 1624–1626.

Dal Canto MB, Mignini Renzini M, Brambillasca F *et al.* 2006 IVM – the first choice for IVF in Italy. *Reproductive BioMedicine Online* **13**, 159–165.

Daya S, Gunby J, Hughes EG *et al*. 1995 Natural cycles for in-vitro fertilization: cost–effectiveness analysis and factors influencing outcome. *Human Reproduction* **10**, 1719–1724.

Duckitt K, Templeton AA 1998 Cancer in women with infertility. *Current Opinion in Obstetrics and Gynecology* **10**, 199–203.

Edwards RG 1965a Maturation *in vitro* of mouse, sheep, cow, pig, rhesus monkey and human ovarian oocytes. *Nature* **208**, 349–351.

Edwards RG 1965b Maturation *in vitro* of human ovarian oocytes. *Lancet* **286**, 926–929.

Edwards RG, Bavister BD, Steptoe PC 1969 Early stages of fertilization *in vitro* of human oocytes matured *in vitro*. *Nature* **221**, 632–635.

Hillier TG 1994 Current concepts of the role of FSH and LH in folliculogenesis. *Human Reproduction* **9**, 188–191.

Janssens RM, Lambalk CB, Vermeiden JPW *et al*. 2000 In-vitro fertilization in a spontaneous cycle: easy, cheap and realistic. *Human Reproduction* **15**, 314–318.

Johnston I, Lopata A, Speirs A *et al*. 1981 In-vitro fertilization: the challenge of the eighties. *Fertility and Sterility* **36**, 699–706.

Jones HW Jr, Jones GS, Andrews MC *et al*. 1982 The program for in-vitro fertilization at Norfolk. *Fertility and Sterility* **38**, 14–21.

Lenton EA, Woodward B 1993 Natural cycle versus stimulated-cycle IVF: is there a role for IVF in the natural cycle? *Journal of Assisted Reproduction and Genetics* **10**, 406–408.

Lim JH, Park SY, Yoon SH, Yang SH *et al*. 2007 Combination of natural cycle IVF with IVM as infertility treatment. In: Tan SL, Chian RC, Buckett WM (eds) *In-vitro Maturation of Human Oocytes, Basic science to clinical application*. Informa Healthcare Press, London, UK. **27**, 353–360.

Lin YH, Hwang JL, Huang LW *et al*. 2003 Combination of FSH priming and hCG priming for in-vitro maturation of human oocytes. *Human Reproduction* **18**, 1632–1636.

Lopata A, Brown JB, Leeton JF *et al*. 1978 In-vitro fertilization of preovulatory oocytes and embryo transfer in infertile patients treated with clomiphene and human chorionic gonadotropin. *Fertility and Sterility* **30**, 27–35.

Lukassen HGM, Kremer JA, Lindeman EJM *et al*. 2003 A pilot study of the efficiency of intracytoplasmic sperm injection in a natural cycle. *Fertility and Sterility* **79**, 231–232.

Nagle F, Sator MO, Juza J, Huber JC 2002 Successful pregnancy resulting from in-vitro matured oocytes retrieved at laparoscopic surgery in a patient with polycystic ovary syndrome. *Human Reproduction* **17**, 373–374.

Nargund G, Waterstone J, Bland JM *et al*. 2001 Cumulative conception and live birth rates in natural (unstimulated) IVF cycles. *Human Reproduction* **16**, 258–262.

Paulson RJ, Sauer MV, Francis MM *et al*. 1994 Factors affecting pregnancy success of human in-vitro fertilization in unstimulated cycles. *Human Reproduction* **9**, 1571–1575.

Pincus G, Enzmann EV 1935 The comparative behavior of mammalian eggs *in vitro* and *in vitro*. I. The activation of ovarian eggs. *Journal of Experimental Medicine* **62**, 665–675.

Pincus G, Saunders B 1939 The comparative behavior of mammalian eggs *in vivo* and *in vitro*. VI. The maturation of human ovarian ova. *Anatomal Record* **75**, 537–545.

Son WY, Yoon SH, Lim JH 2006 Effect of gonadotrophin priming on in-vitro maturation of oocytes collected from women at risk of OHSS. *Reproductive BioMedicine Online* **13**, 340–348.

Son WY, Yoon SH, Lee SW *et al*. 2002 Blastocyst development and pregnancies after in-vitro fertilization of mature oocytes retrieved from unstimulated patients with PCOS after in-vivo HCG priming. *Human Reproduction* **17**, 134–136.

Steptoe PC, Edwards RG 1978 Successful birth after IVF. *Lancet* **312**, 366.

Thornton MH, Francis MM, Paulson RJ 1998 Immature oocytes retrieval: lessons from unstimulated IVF cycles. *Fertility and Sterility* **70**, 647–650.

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