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Case Report

The First Successful Capacitation In Vitro Maturation of Oocyte in Indonesia: A Promising Strategy to Enhance IVF Accessibility for Infertile Couples

Andrew Kan [1], Nining Handayani [2], Arif Sofyan Aziz [1], Pitra Rahmawati [1], Arief Boediono [1, 2, 3], Ivan Sini [1, 2, 3, 4*]

1- Morula IVF Jakarta Clinic, Jakarta, Indonesia
2- IRSI Research and Training Centre, Jakarta, Indonesia
3- Division of Biomedical Sciences, Faculty of Medicine and Nutrition, IPB University, West Java, Indonesia
4- Faculty of Medicine, IPB University, West Java, Indonesia

** Corresponding Author:*
Ivan Sini, Faculty of Medicine and Nutrition, IPB University, West Java, Indonesia
E-mail:
ivan.sini@apps.ipb.ac.id

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Abstract

Background: The identification of c-type natriuretic peptide (CNP) as a key upstream regulator of cyclic GMP (cGMP) levels has paved the way for innovative *in vitro* maturation (IVM) techniques, the so-called biphasic CAPA-IVM (capacitation IVM) approach. This method uses CNP to prevent early meiosis progression and has demonstrated enhanced oocyte maturation rates. This report highlights the successful use of the CAPA-IVM method in Indonesia.

Case Presentation: Immature cumulus-oocyte complexes (COCs) were successfully retrieved from an infertile woman aged 37 years without prior ovarian stimulation. The obtained COCs were incubated in CAPA medium for 24 *hr* and then transferred to a maturation medium containing amphiregulin, insulin, human serum albumin, and recombinant FSH. After 30 *hr*, all immature oocytes reached the metaphase II (MII) stage, as evidenced by the first polar body extrusion and confirmed through spindle formation.

Conclusion: CAPA-IVM system enabled all retrieved immature oocytes to reach the MII stage without prior ovarian stimulation. This finding supports its feasibility as a simplified IVF approach with the potential to reduce treatment costs, particularly in resource-limited settings. However, further clinical evaluation is required to confirm its effectiveness.

Keywords: C-type oocytes, In vitro fertilization, *In vitro* oocyte maturation, Natriuretic peptide.
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Introduction

In vitro maturation (IVM) has been established in various species since 1935 (1). In the early 1960s, Robert Edwards and his colleagues made remarkable efforts to explore IVM as an alternative strategy for treating human infertility (2), with successful applications beginning in 1991 (3, 4). IVM is defined as the retrieval of immature oocytes from 2-10 *mm* follicles from unstimulated or minimally stimulated ovaries, followed by *in vitro* culture until they reach metaphase II (MII) stage (5). Despite significant advances over the years, human oocyte maturation remains challenging due to asynchronous nuclear and cytoplasmic maturation, limiting its efficiency in achieving successful pregnancy compared to conventional IVF. The key to IVM success lies in preserving the integrity of the bidirectional communication structure between cumulus cells and oocytes, particularly through transzonal projections (TZPs) and gap junctions, which play a critical role in oocyte maturation (5). Removal of cumulus-oocyte complex (COC) from the ovary dis-

rupts the flow of meiotic inhibitors, the so-called cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) between cumulus cells and oocytes. As a consequence, phosphodiesterase 3A enzymes are activated, leading to the phosphorylation of connexin proteins within gap junctions. In addition, lower cGMP levels result in the degradation of intra-oocyte cAMP by phosphodiesterase, causing the premature resumption of meiosis.

The breakthrough discovery of a c-type natriuretic peptide (CNP) molecule in regulating cGMP in mouse oocytes (6) and preserving the integrity of the bidirectional communication structure, which in turn controls the activation of phosphodiesterase enzymes and prevents germinal vesicle breakdown, has significant potential to improve the clinical practice of IVM (5). The understanding that CNP/cGMP acts as upstream modulator for cAMP led to the introduction of a biphasic or pre-IVM culture approach in 2015, which has become an established routine IVM known as capacitation IVM (CAPA-IVM) in 2020 (5). This approach has demonstrated pregnancy outcomes that are comparable or superior to those of conventional stimulation in selected patients (7). Briefly, the method consists of a two-step culture of COCs. In step one, culture medium contains CNP as a meiosis inhibitor, preventing precocious meiosis resumption and allowing oocytes to continue mRNA transcription activity, which is crucial in supporting developmental competence. In step two, the culture medium enables the oocyte to resume meiosis.

The first successful conversion of human germinal vesicle (GV) oocytes to mature MII oocytes using the CAPA-IVM system in Indonesia is reported in this paper. COCs were successfully retrieved without ovarian stimulation or the administration of an oocyte maturation trigger.

Case Presentation

A woman aged 37 years presented to our IVF clinic with a 14-year history of primary infertility and irregular menstrual cycles. This patient had a history of poor ovarian response to gonadotropin stimulation across three prior IVF cycles performed at other IVF clinics. Records were available only for the most recent of the three cycles, which was performed in 2017 (Table 1). In her last ovarian stimulation cycle, controlled ovarian stimulation was initiated using a starting gonadotropin dose of 300 *IU* daily for seven days. After seven injections, the clinician determined that the patient had responded poorly to gonadotropin stimulation; therefore, the cycle was discontinued, and the patient was advised to return to the clinic on day 2/3 of her next menstrual period. However, the patient did not return for further treatment at that time. Across all three stimulation cycles, follicular development was inadequate, leading to cancellation of ovum pick-up in each attempt.

In March 2024, as a final attempt to conceive, the patient visited our clinic seeking another possible treatment. Her BMI was within the normal range (20.17 kg/m^2). Ovarian reserve assessment revealed an anti-Mullerian hormone (AMH) level of 4 *ng/ml*, and a basal antral follicle count (AFC) of 20. Baseline hormonal evaluation revealed an estradiol level of 60.29 *pg/ml*, a basal follicle-

Table 1. Baseline and clinical characteristics of the presented case

Baseline clinical characteristics	Third cycle in 2017	March 2024	CAPA-IVM cycle in August 2024
Age (years)	31	37	37
Body mass index (kg/m^2)	-	20.17	20.17
Infertility duration (years)		14	14
AMH (*ng/ml*)	-	4	-
Basal AFC	-	20	8
Basal FSH (*mIU/ml*)	24.4	19	17
Basal LH (*mIU/ml*)	14.32	13.48	18.09
Basal estradiol (*pg/ml*)	<5	60.29	114.8
Basal progesterone (*ng/ml*)	-	0.11	0.26
Starting dose of gonadotropin	300 *IU*	-	-
Number of oocytes retrieved	Cycle canceled due to inadequate ovarian response	-	5 oocytes

stimulating hormone (FSH) level of 19 *mIU/ml*, a basal luteinizing hormone (LH) level of 13.48 *mIU/ml*, and a progesterone level of 0.11 *ng/ml*.

After clinical evaluation, the IVM approach was offered by the clinician in August 2024, considering the patient's suspected gonadotropin resistance. Following approval from the advisory board of the clinic and comprehensive counseling regarding the procedure, potential benefits, and associated risks, the patient consented to undergo ovum pick-up retrieval without ovarian stimulation. Transvaginal ovarian follicle puncture was performed on day 11 of the menstrual cycle. Under mild sedation, eight follicles measuring 2-7 *mm* in diameter, with an average size of 4 *mm*, were seen under ultrasound. A 20-gauge single-lumen IVM needle (Kitazato, Japan) was used to retrieve five immature oocytes. GMOPS medium (Vitrolife, Sweden), supplemented with 50 *nM* CNP (Sigma-Aldrich, USA; Lot No. SLCF0284), 20 *nM* estradiol (Sigma-Aldrich, USA; Cat. No. E1024, Lot No. SLCQ6890), and 10 *mg/ml* human serum albumin (HSA; Vitrolife, Sweden), was used as the aspiration medium. The aspiration medium was supplemented with 50 *nM* CNP to maintain meiotic arrest in the COCs immediately following aspiration and throughout the collection and handling procedures (Figure 1). As estradiol supports the CNP-NPR2 pathway, adding 20 *nM* estradiol would be beneficial for preserving the physiological follicular environment during oocyte retrieval (8). To optimize the search process, follicular fluid was filtered through a cell strainer.

The CAPA-IVM medium was prepared according to the protocol described by Sanchez et al. (9). Briefly, the base medium (Medicult IVM System; Origio, Denmark) was supplemented with 25 *nM* CNP, 10 *mg/ml* human serum albumin (HSA), 1 *mIU/ml* recombinant follicle-stimulating hormone (rFSH; Gonal-f®, Merck Serono, Switzerland), 10 *nM* estradiol, and 5 *ng/ml* insulin (Sigma-Aldrich, USA; Cat. No. I9278). The concentration of 25 *nM* CNP used in the CAPA medium was selected based on previous findings indicating that it is optimal for mimicking the physiological action of CNP. The obtained COCs were incubated in 500 *µl* of CAPA medium covered with mineral oil at 37°*C* and 6% CO_2 for 24 *hr*. Following the pre-IVM culture period, the COCs were washed and transferred to maturation medium (Medicult IVM System; Origio, Denmark) supplemented with 100 *ng/ml* recombinant human amphiregulin (R&D Systems, USA), 5 *ng/ml* insulin (Sigma-Aldrich, USA), 10 *nM* estradiol, 10 *mg/ml* HSA, and 100 *mIU/ml* recombinant follicle-stimulating hormone (rFSH; Gonal-f®, Merck Serono, Switzerland). Oocyte maturation was assessed after 30 *hr* of culture, and all five COCs reached the MII stage, corresponding to a maturation rate of 100% (Figure 2). Detailed evaluation using the OCTAX PolarAIDE™ system confirmed the presence of a meiotic spindle in all mature oocytes (Figure 3).

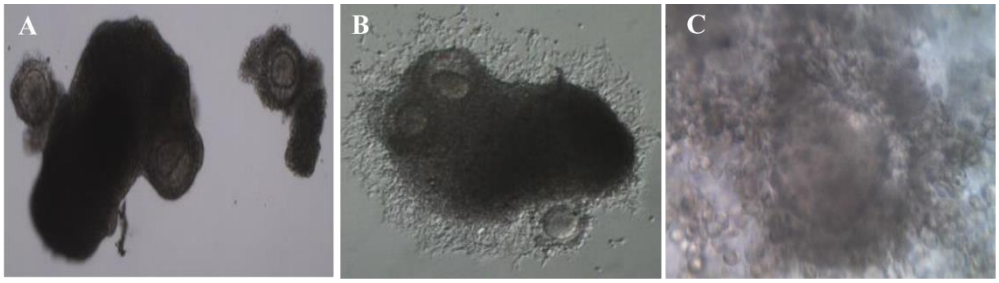

Figure 1. Immature oocyte for CAPA-IVM (A) after ovum pick-up, (B) 24 *hr* post-CAPA-IVM culture, and (C) 24 *hr* post-CAPA-IVM culture

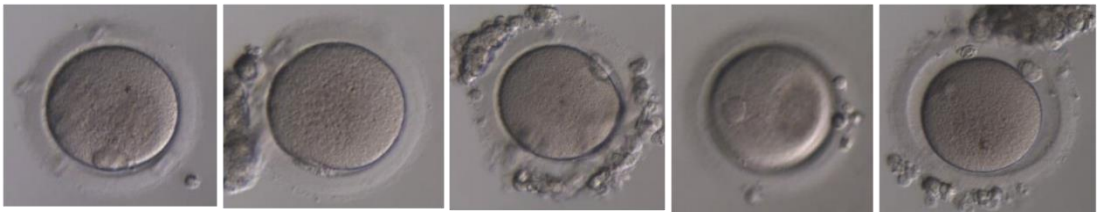

Figure 2. Mature oocyte post-CAPA-IVM

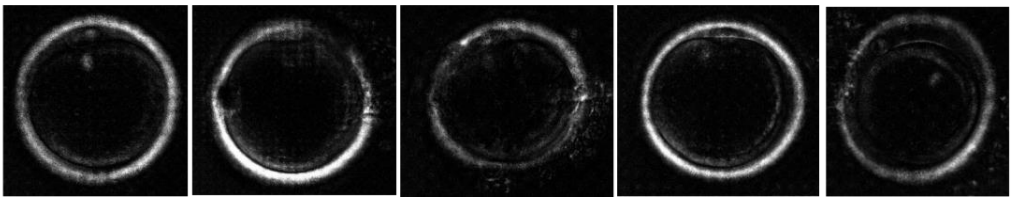

Figure 3. Polarized light microscopy image obtained using the OCTAX PolarAIDE™ system demonstrating a mature MII oocyte with the meiotic spindle positioned at approximately the 12 o'clock position

Ethics approval

Since no intervention was performed in this study, ethical approval is not required. Therefore, investigators may proceed with their publication, provided they maintain the confidentiality and anonymity of the study subject. Written informed consent from the patient was retrieved.

Discussion

In this case, fertilization was unfortunately not performed immediately after IVM because the male partner was unable to provide a semen sample following completion of the IVM procedure. Consequently, all mature oocytes were cryopreserved. However, our results support previous findings indicating that the CAPA-IVM approach improves maturation of oocytes derived from small antral follicles. Sanchez et al. (9) further reported favorable embryological outcomes following CAPA-IVM. Likewise, in a study involving 80 women diagnosed with PCOS, Vuong et al. (10) reported that CAPA-IVM achieved a significantly higher oocyte maturation rate than conventional IVM (63.6% versus 49%, $p<0.001$). As this was our first CAPA-IVM case, predefined eligibility criteria had not been established.

Despite concerns regarding the clinical application of CAPA-IVM, including the need to identify the patients most likely to benefit from the procedure and the relatively high attrition rate during embryo development, the potential benefits of CAPA-IVM remain substantial. In particular, this approach may reduce the cost of treatment by eliminating the need for ovarian stimulation and monitoring, which is a major expense in Indonesia. Therefore, for selected patients, especially those for whom treatment cost is a major concern, successful oocyte maturation through CAPA-IVM may offer a promising alternative. The potential reduction in treatment costs could significantly increase the accessibility and adoption of IVF in Indonesia, which currently lags behind in the number of IVF cycles despite its large population and a GDP per capita similar to that of countries such as Vietnam. Other developed countries, such as Belgium and Australia, have yet to widely adopt CAPA-IVM due to subsidized medication costs and historical concerns. A shift towards drug-free IVF could offer substantial cost savings and encourage broader utilization, particularly in contexts where drug costs are a significant barrier.

Conclusion

This first reported case of CAPA-IVM in Indonesia demonstrates its successful implementation without ovarian stimulation. All retrieved immature oocytes reached the MII stage, as confirmed by polar body extrusion and spindle formation. These findings suggest that CAPA-IVM may offer a simpler and more affordable IVF approach, although further studies are warranted to confirm its clinical effectiveness.

Conflict of Interest

None.

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