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ASSISTED REPRODUCTION TECHNOLOGIES

Development of children born after in vitro maturation with a prematuration step versus natural conception: a prospective cohort study

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Abstract

Purpose IVM preceded by a prematuration step (capacitation [CAPA]-IVM) improves the acquisition of oocyte developmental competence and can enhance embryo quality. There is currently no follow-up data on babies born from CAPA-IVM. This study investigated developmental outcomes in children born after CAPA-IVM versus natural conception.

Methods This prospective cohort study was conducted at a fertility clinic in Vietnam in August/September 2019. Children born after CAPA-IVM were propensity score-matched with those born after natural conception. All parents were asked to complete the Developmental Red Flags and Ages & Stages Third Edition (ASQ-3) questionnaires.

Results A total of 46 parents (23 in each group) of 55 babies (31 CAPA-IVM and 24 natural conception) were included in the study. Baseline characteristics, including mother's age and body mass index, gestational age at delivery, and birth weight, were comparable. The mean age of children at the end of follow-up was 15 months. The overall proportion of children with any abnormal ASQ-3 score was 6.5% in the CAPA-IVM group and 20.8% in the natural conception group ($p = 0.24$). The proportion of children with a developmental red flag did not differ significantly between the CAPA-IVM and natural conception groups (9.7% vs. 4.2%; $p = 0.80$).

Conclusions The use of CAPA-IVM did not have any significant impact on childhood physical and mental development compared with children born as a result of natural conception.

Keywords In vitro fertilization · In vitro maturation · Capacitation · Childhood development · ASQ-3 · Red Flag sign

Background

In vitro maturation (IVM) is an assisted reproductive technology (ART) in which minimally stimulated or unstimulated oocytes are retrieved and then undergo maturation stages in vitro. IVM treatment cycles are mainly indicated for women with a high antral follicle count, especially those with polycystic ovary syndrome (PCOS) [1, 2]. In addition, IVM has a potential role in the setting of several other indications, including poor ovarian reserve or repeated in vitro fertilization (IVF) failures [3]. Because IVM requires no or only mild ovarian stimulation [4, 5], the use of daily human menopausal gonadotropins (hMG) in conventional IVF cycles is eliminated and patient convenience is improved. Although hMG increases the number of oocytes retrieved and the chance of pregnancy, their use can also result in ovarian hyperstimulation syndrome (OHSS) [6]. Therefore, IVM could be widely applied because of its safety, replicability, reduced costs, and patient discomfort, and almost elimination of OHSS risk [7–11].

Although IVM has a number of advantages, implantation and live birth rates after IVM are generally lower than those achieved with IVF [1, 8, 10]. Immature oocyte complexes for IVM are often retrieved from germinal-vesical (GV) stage follicles, which range from 2 to 10 mm in size and are mostly < 6 mm in women with PCOS [12–14]. As

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a result, embryo development and the live birth rate from IVM oocytes are lower than conventional methods [15, 16].

These issues led to the investigation of the value of a prematuration step that precedes IVM to enhance the maturation of oocytes during IVM. This prematuration step involves maintaining the cyclic adenosine monophosphate level in cumulus-oocyte complexes (COCs) after aspiration and in the early stage of oocyte culture, leading to in vitro oocyte capacitation (CAPA), preventing the spontaneous maturation of oocytes in vitro [17]. However, the use of IVM, especially IVM with a prematuration step (CAPA-IVM) at ART centers, is not currently widespread due to the lower live birth rate compared with standard IVF. Moreover, there is currently a lack of follow-up data from babies born after CAPA-IVM meaning that the effects of CAPA-IVM on child development have not been well defined to date.

This study investigated differences in the development of children born after CAPA-IVM compared with those conceived naturally.

Methods

Study design

This prospective cohort study was conducted at IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam, from August 2019 to September 2019. The study was approved by the institutional Medical Ethics Committee (08/19/ĐĐ-BVMĐ) on August 1st, 2019. The trial was conducted according to Good Clinical Practice and Declaration of Helsinki 2002 principles. Parents of children born alive provided informed consent for participation in the follow-up study.

Study population

This study included babies born to women who had undergone CAPA-IVM and those conceived naturally between July 2017 and December 2018 (aged 1 to 66 months at follow-up). Sperm and oocyte donation cycles were excluded, as were babies whose parents declined to provide informed consent. Propensity score matching was used to match babies born after natural conception with those born after CAPA-IVM based on the mother's age and gestational age at delivery.

CAPA-IVM protocol

Patients in the CAPA-IVM group underwent ovarian priming with recombinant follicle-stimulating hormone (rFSH). rFSH 150 IU/day was given for 3 days starting from the second day of the woman's menstrual period. Oocyte pick-up was scheduled at 42–46 h after the last injection of rFSH. Cumulus-oocyte complexes (COCs) from follicles with diameters of < 6 mm and ≥ 6 mm were retrieved and cultured separately in a prematuration medium with C-type natriuretic peptide followed by CAPA-IVM. Full details of the CAPA-IVM protocol used in the study have been previously reported [18]. No embryos were biopsied and checked for aneuploidies prior to vitrification, which took place on day 3 (cleavage stage) after intracytoplasmic sperm injection (ICSI) for all embryos (a freeze-all strategy). Women received oral estradiol valerate (Valiera®, Laboratorios Recalcine) 2 mg 4 times daily from day 2 of their menstrual cycle. After ≥ 10 days' treatment with estradiol valerate and when endometrial thickness was ≥ 8 mm, progesterone (Cyclogest®, Actavis) 200 mg was administered intravaginally 4 times daily. Embryo transfer was scheduled 3 days after starting progesterone. Luteal phase support was given until the day of pregnancy testing and continued at the same dosage until at least 11 weeks of pregnancy.

Assessments

Babies who met the inclusion criteria and their legal guardians were invited to My Duc Hospital to undergo an assessment of the children's physical, mental, and locomotor states by a pediatrician. Families who could not attend the clinic for direct evaluation were sent consent forms, questionnaires, and detailed instructions via postal mail and e-mail. Completed questionnaires were returned via postal mail, e-mail, or instant messenger.

Mental and locomotor states were evaluated using the Vietnamese version of the Ages & Stages Questionnaires® Third Edition (ASQ-3). The ASQ-3 is designed to detect a developmental delay in children and covers five developmental areas: communication, gross motor, fine motor, problem solving, and personal-social. Each area consists of six questions, which are assigned a score of 0 (not yet), 5 (sometimes), or 10 (yes). Each domain includes six questions that are scored as 0 (not yet able), 5 (sometimes able), or 10 (fully able), with a maximum total score of 60 (lower scores indicate less attainment of developmental milestones). The maximum total score is 60, with lower scores indicating less attainment of developmental milestones [19]. Abnormality is defined as a score > 2 standard deviations below the mean, with a sensitivity of 0.86, specificity of 0.86, false positive and false negative rates of 0.14, an under-identified rate of 0.06, and an over-identified rate of 0.08 [19]. A Vietnamese version of the ASQ-3 has been validated by an expert committee and is widely used in local clinical practice. Scores were adjusted for child age.

The Red Flags questionnaire was designed by the US Centers for Disease Control and Prevention to provide

healthcare professionals working with young children (up to 6 years of age) and their families with a quick reference guide to help identify children at risk of not meeting his/her health and/or developmental milestones [20]. The Red Flags questionnaire used in this study was composed of five items for children from 1 to < 2 years old: not able to say consonant sounds by the age of 15 months; not able to imitate others by the age of 16 months; not able to point a finger to things they are interested in; not presenting the dominant and non-dominant hand by the age of 18 months; not able to walk up and downstairs by the age of 24 months; not able to use repetitive words of others mechanically; and not able to achieve the milestone of 50 single words usage by the age of 24 months. The presence of any red flag suggests developmental disorders. All children who showed abnormalities during any study-related assessments were checked by a pediatrician.

Outcomes

The primary outcome of this follow-up analysis was the proportion of abnormal ASQ-3 and Red Flag scores for all live births after CAPA-IVM versus natural conception. Secondary outcomes were the abnormal ASQ-3 rate in each category and factors influencing presentation with an abnormal ASQ-3 score.

Statistical analysis

Data were analyzed using descriptive statistics (mean and standard deviation for normally distributed variables, or median and interquartile range for skewed variables). Differences between groups were analyzed using Fisher's exact test for categorical variables, Student's *t*-test for normally distributed continuous variables, and Mann–Whitney test for skewed variables. Scores on the Red Flags and ASQ-3 questionnaires were analyzed using descriptive statistics and compared between groups using Wilcoxon's test or Fischer's exact test; 95% confidence interval (CI) values for between-group differences were calculated using the bootstrap method. A cluster analysis was performed to compare the Red Flags and ASQ-3 scores of twins between the CAPA-IVM and normal conception groups. All analyses were performed using the R statistical packages (R version 3.3.3). Statistical significance was defined as $p < 0.05$.

Results

Parents

The number of babies born after CAPA-IVM at My Duc Hospital between July 2017 and December 2018 was 31 (from 23 women). After propensity score matching, the natural conception group included 24 babies from 23 women. One parent declined to give information, and none was excluded due to egg donation. Three of 23 parents in the CAPA-IVM group and five of 23 parents in the natural conception group could not attend the clinic and provide their responses via questionnaires. There were no significant differences in demographic characteristics between the two groups, but the rate of twins was significantly higher in the CAPA-IVM versus natural conception group (34.8% vs. 4.3%, respectively, $p = 0.026$) (Table 1). Mean age of children at the end of follow-up was 15 months.

Outcomes

The proportion of babies with any abnormal ASQ-3 score was numerically lower in the CAPA-IVM group (6.5%) compared with babies conceived naturally (20.8%), but the between-group difference did not reach statistical significance ($p = 0.238$) (Table 2). Conversely, the proportion of babies with a developmental red flag was higher in the CAPA-IVM versus natural conception group (9.7% vs. 4.2%, respectively), but again this was not statistically significant ($p = 0.797$) (Table 2). All children with red flags were sent for specialist check-up and found to be normal. No significant predictors of abnormal ASQ-3 score were identified in the univariate or multivariate analyses (Table 3).

Discussion

This study was the first follow-up analysis using the ASQ-3 score to evaluate the development of babies conceived using CAPA-IVM. The results showed no statistically significant differences in physical and mental childhood development in children born after CAPA-IVM compared with those who were conceived naturally.

Our findings are consistent with those of a previous study in which children born to mothers with PCOS to had undergone priming for oocyte retrieval, IVM, ICSI, and embryo transfer were compared with naturally conceived children using the Bayley Scales of Infant Development to evaluate mental and motor development [21]. We used a different approach to the assessment of infant development—the ASQ-3. These questionnaires are validated and widely used to evaluate infant development across many domains (communication, gross motor, fine motor, problem solving, and personal-social skills) [22, 23]. Although used different assessments, there were also a number of important similarities between our study and the previous trial by Shu-Chi et al. [21]. Baseline

Table 1 Baseline demographics and clinical characteristics for women and their babies

Characteristics	CAPA-IVM ($n=23$)	Natural conception ($n=23$)	p value
Age, years	29.5 ± 3.9	29.4 ± 3.8	0.939
Body mass index, kg/m^2	21.1 ± 0.9	21.0 ± 0.4	0.534
Anti-Müllerian hormone, ng/mL	12.2 ± 4.4	–	
Duration of infertility, years	3.0 ± 2.0	–	
Number of previous IVF attempts, *n* (%)			
1	22 (95.7)	–	
≥ 2	1 (4.3)	–	
Type of infertility, *n* (%)			
Primary	13 (56.5)	–	
Secondary	10 (43.5)	–	
IVF indication, *n* (%)			
Male factor	1 (4.3)	–	
PCOS	21 (91.3)	–	
Low ovarian reserve	1 (4.3)	–	
Tubal factor	0 (0.0)	–	
Unexplained	0 (0.0)	–	
Type of delivery, *n* (%)			
Cesarean	20 (87.0)	23 (100.0)	0.232
Spontaneous	3 (13.0)	0 (0.0)	
Gestational age at delivery, weeks	37.2 ± 1.2	37.9 ± 1.2	0.055
Gestational age > 37 weeks, *n* (%)	11 (47.8)	12 (52.2)	0.987
Gestational age 34–37 weeks, *n* (%)	12 (52.2)	11 (47.8)	0.899
Gestational age < 34 weeks, *n* (%)	0 (0.0)	0 (0.0)	–
Twins, *n* (%)	8 (34.8)	1 (4.3)	0.026
Birth weight, g			
Singleton	3206.7 ± 435.0	3031.8 ± 363.0	0.193
Twin	2536.3 ± 378.4	2250.0 ± 212.1	0.318
NICU admission, *n* (%)	7 (22.6)	6 (25.0)	0.999
Singleton	5/15 (33.3)	4/22 (18.2)	0.506
Twin	2/16 (12.5)	2/2 (100.0)	0.057
Neonatal composite, *n* (%)	6 (26.1)	4 (16.7)	0.994
Singleton	4/15 (26.7)	4/22 (18.2)	0.999
Twin	2/16 (12.5)	0/2 (100)	0.989

Values are mean ± standard deviation, or number (%)

CAPA, Capacitation; IVF, *in vitro* fertilization; IVM, *in vitro* maturation; NICU, neonatal intensive care unit; PCOS, polycystic ovary syndrome

demographics of the mothers and mean birthweights in both studies were similar, as was the age of children at follow-up. Different IVM protocols were used but taken together, data from these two studies suggest that IVM does not appear to have any negative effects on the mental and physical development of children conceived using this procedure.

One interesting finding from our study was that although mean birthweight was not significantly different between the IVM and natural conception groups, values were numerically higher in the CAPA-IVM versus natural conception group (Table 1). Higher birthweight has previously been reported in infants conceived using IVM [24, 25], which is something that warrants additional research.

To determine whether any other factors influenced a child's abnormal ASQ score, we performed univariate and multivariate analyses for the whole study population, incorporating factors that could potentially influence childhood development (Table 3). Type of conception, along with maternal age and body mass index, gestational age at delivery, birth weight, and admission to the

Table 2 Ages and Stages Questionnaire findings in children

	CAPA-IVM ($n=31$)	Natural conception ($n=24$)	p value
Age at completion of follow-up, months	15.0 ± 4.1	15.0 ± 4.6	0.978
Singleton	15.9 ± 4.4	15.1 ± 4.8	0.621
Twin	14.3 ± 3.8	14.0 ± 0.0	0.929
Body weight at completion of follow-up, kg	9.9 ± 1.4	10.3 ± 1.3	0.263
Singleton	10.5 ± 1.5	10.3 ± 1.3	0.716
Twin	9.3 ± 1.0	10.0 ± 0.2	0.372
Abnormal ASQ-3 scores, *n* (%)			
Communication	0 (0.0)	2 (8.3)	0.362
Singleton	0/15 (0.0)	2/22 (9.1)	0.645
Twin	0/16 (0.0)	0/2 (0.0)	–
Gross motor	0 (0.0)	1 (4.2)	0.897
Singleton	0/15 (0.0)	1/22 (4.5)	0.999
Twin	0/16 (0.0)	0/22 (0.0)	–
Fine motor	2 (6.5)	1 (4.2)	0.999
Singleton	2/15 (13.3)	1/22 (4.5)	0.728
Twin	0/16 (0.0)	0/2 (0.0)	–
Problem solving	1 (3.2)	0 (0.0)	0.999
Singleton	1/15 (6.7)	0/22 (0.0)	0.845
Twin	0/16 (0.0)	0/2 (0.0)	–
Personal social	0 (0.0)	2 (8.3)	0.362
Singleton	0/15 (0.0)	2/22 (9.1)	0.645
Twin	0/16 (0.0)	0/2 (0.0)	–
Overall	2 (6.5)	5 (20.8)	0.238
Singleton	2/15 (13.3)	5/22 (22.7)	0.773
Twin	0/16 (0.0)	0/2 (0.0)	–
Developmental Red Flag, *n* (%)			
Overall	3 (9.7)	1 (4.2)	0.797
Singleton	3/15 (20.0)	1/22 (4.5)	0.344
Twin	0/16 (0.0)	0/2 (0.0)	–

Values are mean ± standard deviation, or number (%)

ASQ-3, Ages & Stages Third Edition Questionnaire; CAPA, capacitation; IVM, *in vitro* maturation

neonatal intensive care unit all failed to show a significant association with abnormal ASQ-3 score in these analyses. This provides further support for the lack of any negative effect of CAPA-IVM on childhood physical and mental development.

Although this study provides important initial data on childhood development after CAPA-IVM compared with natural conception, there are a number of limitations that need to be taken into account when interpreting our data. The sample size was small, which limits statistical power for between-group comparisons. In addition, and probably not surprisingly, there were significantly more twin deliveries in the CAPA-IVM group compared with the natural conception group. Twenty-two of the 23 women in the CAPA-IVM group had two embryos transferred and eight delivered twins, compared with only one twin delivery in the natural conception group. Twin delivery is a confounding factor that could have influenced a number of outcomes, including rate of premature birth and infant birthweight. Another potential confounding variable is the fact that nearly all women in the CAPA-IVM group had PCOS. There is the potential for potential health issues in children born to mothers with PCOS undergoing IVM [26], and therefore, a better way to evaluate the effects of CAPA-IVM on childhood development would be to compare similar patient groups (i.e., outcomes in PCOS women who underwent CAPA-IVM and those who conceived naturally). Furthermore, the lean, single ethnicity PCOS population in the CAPA-IVM group could limit the external generalizability of the study findings.

Table 3 Abnormal Ages and Stages Questionnaire findings in patient subgroups

Variables	ASQ-3 scores		OR (95% CI); *p* value	
	Abnormal ($n=7$)	Normal ($n=48$)	Univariate	Multivariate
Group, *n* (%)				
Natural conception	5 (71.4)	19 (39.6)	Ref	Ref
CAPA-IVM	2 (28.6)	29 (60.4)	0.26 (0.03–1.35); 0.131	0.22 (0.03–1.24); 0.105
Maternal age, years	27.8 ± 5.2	29.8 ± 3.4	0.86 (0.67–1.09); 0.226	
Maternal BMI, kg/m^2	21.2 ± 0.8	21.0 ± 0.8	1.37 (0.46–4.05); 0.569	
Twins, *n* (%)	0 (0.0)	18 (37.5)	–	
Gestational age at delivery, weeks	37.1 ± 1.0	37.4 ± 1.3	0.81 (0.40–1.53); 0.521	
Gestational age at delivery > 37 weeks, *n* (%)	1 (14.3)	23 (47.9)	Ref	Ref
Gestational age at delivery 34–37 weeks, *n* (%)	6 (85.7)	25 (52.1)	5.52 (0.85–108.46); 0.126	6.03 (0.76–131.37); 0.136
Birth weight, g				
Singleton	3171.4 ± 546.9	3086.7 ± 364.6	1.06 (0.85–1.32); 0.608	
Twin	0	2504.4 ± 370.9	–	
NICU admission, *n* (%)	3 (42.9)	10 (20.8)	2.85 (0.50–15.10); 0.214	1.58 (0.22–10.19); 0.633

ASQ-3, Ages & Stages Third Edition Questionnaire; BMI, body mass index; CAPA, capacitation; CI, confidence interval; IVM, *in vitro* maturation; NICU, neonatal intensive care unit; OR, odds ratio; Ref, reference

Conclusions

The findings of this study suggest that the mental health and motor development of babies born after CAPA-IVM may be comparable to those of naturally conceived children.

Author contribution This study was designed by Lan N. Vuong, Nghia A. Nguyen, and Toan D. Pham, and was undertaken by Nghia A. Nguyen and Minh H. N. Nguyen. Data were analyzed by Toan D. Pham and all authors were involved in critical discussion of results. Duy L. Nguyen, Toan D. Pham, and Lan N. Vuong wrote the manuscript, which was reviewed and approved by all authors.

Data availability The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

Declarations

Competing interests Lan N. Vuong has received speaker and conference fees from Merck; grant, speaker, and conference fees from Merck Sharpe and Dohme; and speaker and conference fees from Ferring. Duy L. Nguyen, Nghia A. Nguyen, Toan D. Pham, and Minh H. N. Nguyen have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

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