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Follicular fat: Soluble vitamins as markers of oocyte competency

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Abstract

Background: Nearly 10% of people worldwide are infertile. Oocyte developmental competency affects IVF results. Research suggests that fat-soluble vitamin content in follicular fluid affects oocyte and embryo quality.

Aim of study: To investigate the effect of the concentration of fat-soluble vitamins A, D, E, and K in individual follicles on oocyte quality and developmental competence.

Patient and Methods: A 10-month prospective research at Kamal Al-Samarraee Hospital for infertility and IVF in Baghdad, Iraq, from January 1 to November 1, 2024. Sixty infertile women aged 18-38 with fresh cycles entered the infertility consultation room and underwent GnRH antagonist IVF-ICSI cycles. An antagonist GnRH regimen was created for all patients. After controlled ovarian stimulation on oocyte retrieval day, ELISA evaluated serum and follicular fluid vitamins A, D, E, and K.

Results: The pregnancy results of 60 patients were positive in 19 patients, giving a pregnancy rate of 31.7%. A significant association between follicular fluid levels of vitamins A and E and pregnancy status. Vitamin A in follicular fluid was significantly associated with the embryo's top-quality status on day 2. Except for vitamin K, the concentrations of other vitamins in follicular fluid were significantly associated with the embryo development status on the 3rd day of culture, and they were significantly associated with the embryo development status on the 5th day 5 of culture.

Conclusion: By combining routine morphological evaluation with follicular fluid vitamin analysis, it may be possible to select a better embryo for transfer, potentially increasing the likelihood of pregnancy, and determine embryonic developmental competence in a more sensitive and accurate manner.

Keywords: Infertility, pregnancy, ICSI, vitamins, fat-soluble, Iraq

Introduction

Infertility is a significant medical condition that affects individuals and couples worldwide, causing psychological, physical, mental, spiritual, and medical distress. It is estimated that 48.5 million couples experienced infertility in 2010, with 3.5 million cases reported in the UK [1]. Infertility impacts both partners and requires a joint approach for diagnosis and treatment. Approximately 20% of infertility cases are due to male factors alone, while 30-40% involve a male component [2]. Unexplained infertility accounts for 30% of cases, requiring assessment of ovulation, tubal patency, and semen analysis [3]. Assisted reproductive techniques (ART) have significantly improved conception chances for infertile couples [4]. The World Health Organization (WHO) defines infertility as the inability to conceive after 12 months or more of regular, unprotected sexual intercourse [5, 6]. Infertility affects nearly 10% of the global population and is ranked as the fifth highest serious disability among young people [7]. It is a costly condition with implications for individual human rights [8]. In the UK, fertility issues impact one in seven couples, with conception rates decreasing with female age [9]. Worldwide, infertility rates are higher in Eastern Europe, North Africa, and the Middle East [10]. Discrepancies in prevalence are linked to environmental, cultural, and socioeconomic factors [11]. Infertility is classified into primary and secondary infertility. Primary infertility is the inability to conceive after two years of unprotected intercourse among women aged 15-49 years, while secondary infertility occurs when a woman, having previously conceived, fails to do so again within one year [12]. The etiology of infertility includes male and female factors, each contributing to approximately 35% of cases, with combined factors accounting for 20% [13]. Female infertility causes include cervical [14], uterine [15], endometrial [16], tubal [17], and ovulatory factors [18], as well as immunological [19], infectious [20], and hormonal causes [21]. Lifestyle factors such as stress, obesity, smoking, alcohol, and environmental toxins also contribute to infertility [22]. Diagnosis includes a comprehensive history, physical examination, ovulatory function assessment [23], ovarian reserve tests [24], tubal evaluation [25], and laparoscopic investigation. Treatment options include medical therapy [26], ART [27], and surgical interventions [28]. ART techniques such as IVF, ICSI, and gamete intra-fallopian transfer (GIFT) have revolutionized infertility management [29]. Emerging research highlights the role of fat-soluble vitamins in follicular fluid, suggesting their influence on oocyte quality and embryo development in ART [30]. This review explores the causes, diagnosis, and treatment of infertility, emphasizing ART advancements and potential improvements through nutritional and hormonal interventions. Aim of study to investigate the effect of the concentration of fat-soluble vitamins A, D, E, and K in individual follicles on oocyte quality and developmental competence.

Methods

This prospective study was conducted at the infertility outpatient clinic, operating room, and embryology lab of Kamal Al-Samarraee Hospital for Infertility and IVF in Baghdad, Iraq, over 10 months (January 1 - November 1, 2024). Sixty infertile females aged 18-38 years undergoing fresh IVF-ICSI cycles with a GnRH antagonist protocol were included. Verbal consent was obtained.

Exclusion Criteria: endocrine disorders, recurrent miscarriage, azoospermia, frozen cycles, and endometriosis. Patients underwent a detailed history, general and obstetric examination, BMI calculation, and transvaginal ultrasound. Hormonal tests (FSH, LH, E2, AMH, Prolactin, TSH, T3, T4) were performed on cycle day two, along with semen analysis of their husbands. Ovarian response was determined using AMH and antral follicle counts. Controlled ovarian stimulation began on cycle day two. GnRH antagonist was initiated when the largest follicle reached 13-14 mm, continuing until the trigger day. When follicles reached 17-18 mm, either hCG (10,000 IU) or GnRH agonist (0.1 mg) was administered depending on ovarian response. Oocyte retrieval occurred 36 hours' post-trigger. Sperm samples were provided, and intracytoplasmic sperm injection (ICSI) was performed. Embryo transfer occurred on day 3 or day 5 based on embryo quality, with 1-3 embryos transferred per patient. Luteal support with progesterone suppositories (Cyclogest 400 mg) continued for 14 days' post-transfer. Primary outcomes: ovarian response, retrieved oocytes, mature oocytes, viable embryos.
Secondary outcomes: fertilization rate, gonadotropin duration and dose, hormone levels, implantation, and pregnancy rates. Serum and follicular fluid samples were collected pre-stimulation and on oocyte retrieval day, with vitamins A, D, E, and K measured using ELISA. SPSS version 25 was used for data analysis. Continuous variables were compared using the independent t-test, Pearson's correlation assessed relationships, and logistic regression identified predictors of ICSI outcomes. P-values < 0.05 were considered significant. Verbal consent was obtained, and confidentiality was maintained. Approvals were granted by the Council of Arab Board of Medical Specialization.

Results

This study included a total of 60 infertile women. All of them were undergoing ICSI. The age range of the studied women was 24 to 41 years with a mean of 33.07 ± 5.24. Less than half of the patients were in the age group of ≥ 35 years, 29 (48.3%), while 10 (16.7%) and 21 (35%) belonged to the age group of < 30 years and 30 - 34 years, respectively. As illustrated in (Figure 1).

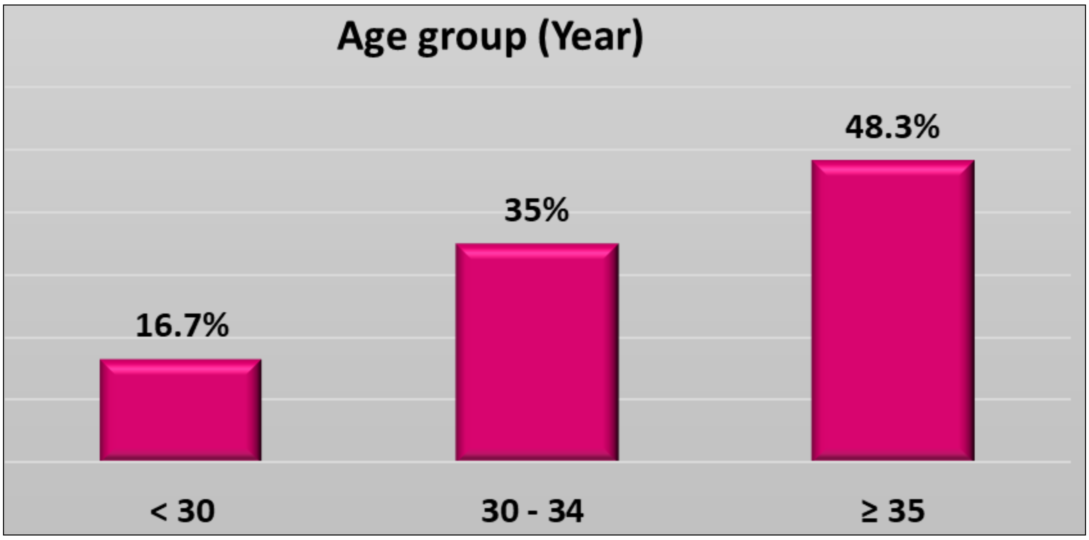

Fig 1: Distribution of the study patients according to age group

Of the 60 enrolled women, more than half 32 (53.3%) had normal BMI levels, 41 (68.3%) suffered from primary infertility, 5 - 9 years was the most common duration of infertility in 25 patients (41.7%), and male factor was the most frequent cause of infertility in 19 women (31.7%). As shown in (Table 1).

Table 1: Sociodemographic and disease-related characteristics

Variable	No. (n= 60)	Percentage (%)
BMI level		
Normal	32	53.3
Overweight	19	31.7
Obese	9	15.0
Type of infertility		
Primary	41	68.3
Secondary	19	31.7
Duration of infertility (Year)		
1 - 4	18	30.0
5 - 9	25	41.7
≥ 10	17	21.3
Cause of infertility		
Male factor	19	31.7
Tubal factor	10	16.7
Low AMH	14	23.3
Ovulatory disorders	9	15.0
Unexplained	8	13.3

The pregnancy results of 60 patients were positive in 19 patients, giving a pregnancy rate of 31.7%, and it was negative in 41 patients (68.3%) as illustrated in (Figure 2).

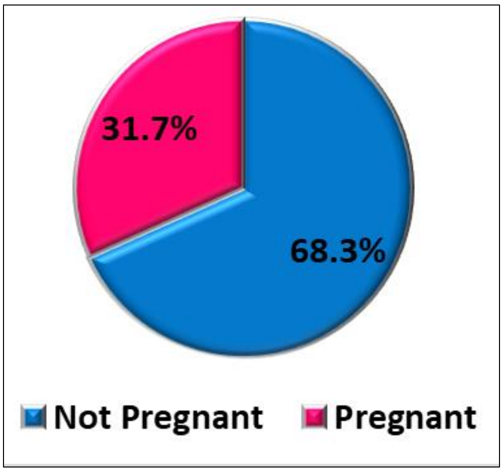

Fig 2: Distribution of study patients according to pregnancy status

The embryo's top quality on day 2 was 38.3%, while the embryo development rates on day 3 and day 5 were 26.7% and 16.7%, respectively. As illustrated in (Figure 3).

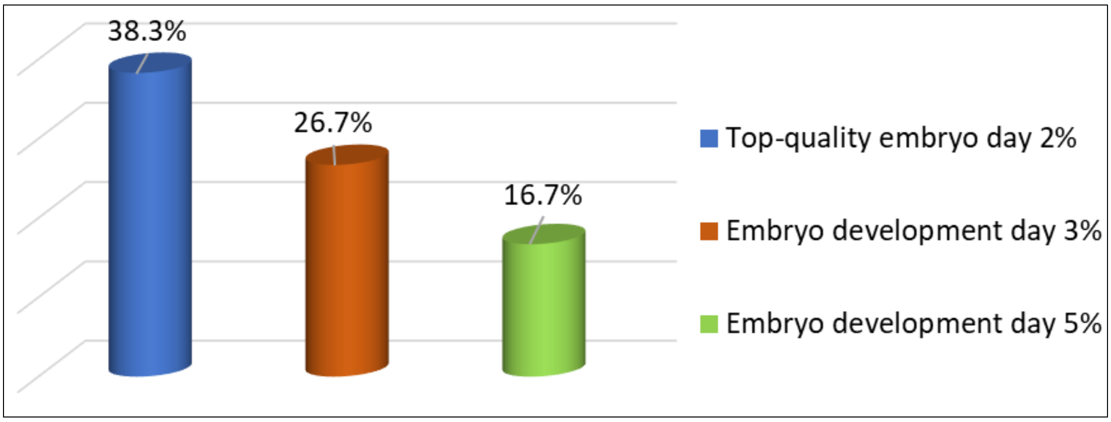

Fig 3: Distribution of study patients according to oocyte quality

In this study, there was a statistically significant association between pregnancy status and the patient's age, type of infertility, and duration of infertility. The rate of pregnancy failure was significantly higher in patients aged ≥ 35 years (86.2%, P= 0.012), had primary infertility (80.5%, P= 0.002), and in patients with infertility for > 10 years' duration (94.1%, P= 0.024). BMI level and cause of infertility showed no significant association with pregnancy status (P ≥ 0.05) as shown in (Table 2).

Table 2: Association between pregnancy status and baseline characteristics

Patients' characteristics	Pregnancy status		Total No. (%)	P - Value
	Pregnant No. (%)	Not pregnant No. (%)		
Age (Year)				
< 30	4 (40.0)	6 (60.0)	10 (16.7)	0.012
30 - 34	11 (52.4)	10 (47.6)	21 (35.0)	
≥ 35	4 (13.8)	25 (86.2)	29 (48.3)	
BMI level				
Normal	11 (34.4)	21 (65.6)	32 (53.3)	0.83
Overweight	5 (26.3)	14 (73.7)	19 (31.7)	
Obese	3 (33.3)	6 (66.7)	9 (15)	
Type of infertility				
Primary	8 (19.5)	33 (80.5)	41 (68.3)	0.002
Secondary	11 (57.9)	8 (42.1)	19 (31.7)	
Duration of infertility (Year)				
< 5	8 (44.4)	10 (55.6)	18 (30.0)	0.024
5 - 9	10 (40.0)	15 (60.0)	25 (41.7)	
≥ 10	1 (5.9)	16 (94.1)	17 (28.3)	
Cause of infertility				
Male factor	6 (31.6)	13 (68.4)	19 (31.7)	0.773
Tubal factor	4 (40)	6 (60)	10 (16.7)	
Low AMH	5 (35.7)	9 (64.3)	14 (23.3)	
Ovulatory disorders	3 (33.3)	6 (66.7)	9 (15)	
Unexplained	1 (12.5)	7 (87.5)	8 (13.3)	

The comparison of hormonal parameters according to pregnancy status showed that the mean AMH level was significantly lower in women who didn't get pregnant compared to those who had pregnancy (1.49 ng/ml vs 2.91 ng/ml, P= 0.001). Other hormones revealed no significant differences ($p \geq 0.05$) regarding clinical pregnancy as illustrated in (Table 3).

Table 3: Comparison of hormonal parameters according to pregnancy status

Hormonal Parameter	Pregnancy status		P - Value
	Pregnant Mean ± SD	Not pregnant Mean ± SD	
LH (IU/L)	6.64 ± 2.04	6.23 ± 2.14	0.486
FSH (IU/L)	7.01 ± 1.19	8.02 ± 2.43	0.092
Prolactin (ng/ml)	14.29 ± 3.97	13.89 ± 4.42	0.736
Progesterone (ng/ml)	1.74 ± 0.81	1.68 ± 0.72	0.773
AMH (ng/ml)	2.91 ± 1.63	1.49 ± 0.98	0.001
Estradiol (pg/ml)	227.4 ± 67.11	264.9 ± 89.07	0.109

The comparison of clinical parameters according to pregnancy status revealed no statistically significant differences (P ≥ 0.05) in the means of endometrial thickness, number of growing follicles, and number of ruptured follicles according to pregnancy status as illustrated in (Table 4).

Table 4: Comparison of clinical parameters according to pregnancy status

Clinical Parameter	Pregnancy status		P - Value
	Pregnant Mean ± SD	Not pregnant Mean ± SD	
Endometrial Thickness (mm)	9.41 ± 1.47	8.65 ± 1.43	0.306
Number of growing follicles	6 ± 3.25	5.67 ± 2.89	0.221
Number of ruptured follicles	0.8 ± 1.31	0.54 ± 0.85	0.571

The present study showed no significant differences in all embryological outcomes according to pregnancy status (P ≥ 0.05) as illustrated in (Table 5).

Table 5: Comparison of embryological outcomes according to pregnancy status

Clinical Parameter	Pregnancy status		P - Value
	Pregnant Mean ± SD	Not pregnant Mean ± SD	
Endometrial Thickness (mm)	9.41 ± 1.47	8.65 ± 1.43	0.306
Number of growing follicles	6 ± 3.25	5.67 ± 2.89	
Number of ruptured follicles	0.8 ± 1.31	0.54 ± 0.85	0.571
Number of oocytes retrieved	5.89 ± 2.52	4.56 ± 2.67	0.076
Number of fertilized oocytes	3.11 ± 2.15	2.38 ± 2.03	0.094
Number of GV oocyte	2.0 ± 1.9	0.82 ± 1.8	0.101
Number of MII oocyte	6.0 ± 2.4	6.55 ± 3.1	0.292
Number of MI oocyte	1.17 ± 1.3	1.3 ± 1.1	0.25
Number of embryos	5.9 ± 3.4	4.31 ± 3.5	0.217
Embryo grade I	2.73 ± 1.8	2.79 ± 1.4	0.314
Embryo grade II	1.6 ± 0.82	2.65 ± 1.91	0.39
Embryo grade III	3.5 ± 1.14	2.0 ± 1.20	0.059
Gonadotrophin total dose (IU)	2187.8 ± 455.2	2101.5 ± 390.2	0.126

The mean serum level of vitamin A was 0.64 ± 0.16 vs 0.92 ± 0.19 for follicular fluid level. Regarding vitamin D, the mean serum level was 25.31 ± 8.28 vs 29.62 ± 10.27 for follicular fluid level. The mean vitamin E level in serum was 4.29 ± 1.42 vs 2.07 ± 1.03 in follicular fluid. The serum and follicular fluid levels of vitamin K were 1.23 ± 0.46 vs 0.79 ± 0.31, respectively as shown in (Figure 4).

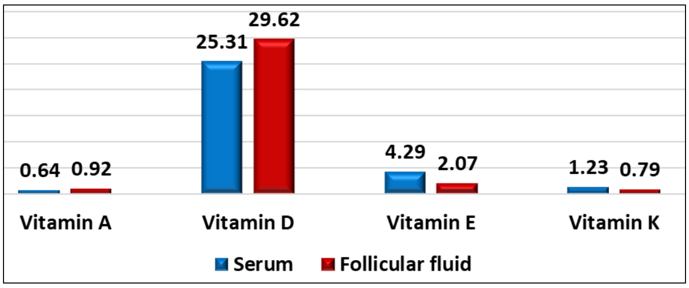

Fig 4: Serum and follicular fluid levels of fat-soluble vitamins

According to Pearson correlation, there were strong positive correlations between serum and follicular fluid of vitamin A (r= 0.703, P= 0.001), vitamin D (r= 0.894, P= 0.001), vitamin E (r= 0.768, P= 0.001), and vitamin K (r= 0.813, P= 0.001) as illustrated in (Table 6).

Table 6: The correlations of fat-soluble vitamins in serum and follicular fluid

Fat-soluble vitamin	Correlation coefficient (r)	P- value
Vitamin A	0.703	0.001
Vitamin D	0.894	0.001
Vitamin E	0.768	0.001
Vitamin K	0.813	0.001

This study found a significant association between follicular fluid levels of vitamins A and E and pregnancy status (OR= 2.41, P= 0.002; and OR= 5.63, P= 0.026), while other vitamins showed no significant association ($p \geq 0.05$). The level of vitamin A in follicular fluid was significantly associated with the embryo's top-quality status on day 2 (OR= 9.18, P= 0.001). On the other hand, the follicular fluid of vitamins D, E, and K revealed no significant association. Except for vitamin K, the concentrations of other vitamins in follicular fluid were significantly associated with the embryo development status on the 3rd day of culture (vitamin A: OR= 11.74, P= 0.004; vitamin D: OR= 2.45, P= 0.003; vitamin E: OR= 3.32, P= 0.001), and they were significantly associated with the embryo development status on the 5th day 5 of culture (vitamin A: OR= 5.37, P= 0.007; vitamin D: OR= 1.26, P= 0.012; vitamin E: OR= 1.87, P= 0.010) as shown in (Table 7).

Table 7: Association between vitamin concentrations in follicular fluid and clinical outcomes of ICSI

Fat-soluble vitamins in follicular fluid	Wald statistic	Odds ratio	95% C.I.		P - Value
			lower	upper	
Clinical pregnancy					
Vitamin A	6.92	2.41	1.35	3.88	0.002
Vitamin D	2.27	1.33	0.93	1.45	0.078
Vitamin E	4.68	5.63	1.94	6.26	0.026
Vitamin K	2.71	1.96	0.73	5.83	0.134
Top-quality embryo day 2					
Vitamin A	7.41	9.18	1.95	23.57	0.001
Vitamin D	0.62	1.03	0.78	1.25	0.224
Vitamin E	0.27	0.84	0.73	1.12	0.671
Vitamin K	1.64	0.54	0.22	1.74	0.423
Embryo development day 3					
Vitamin A	5.26	11.74	1.55	28.8	0.004
Vitamin D	4.43	2.45	1.01	3.64	0.003
Vitamin E	8.97	3.32	1.67	4.02	0.001
Vitamin K	0.91	2.57	0.81	6.64	0.219
Embryo development day 5					
Vitamin A	6.19	5.37	3.45	31.4	0.007
Vitamin D	5.93	1.26	1.18	1.47	0.012
Vitamin E	4.75	1.78	1.05	3.07	0.01
Vitamin K	0.62	0.89	0.56	3.78	0.542

In the present study, statistically significant negative correlations were detected between the vitamin A and D concentrations in follicular fluid and the score of the embryo on the 5th day of culture (r= - 0.383, P= 0.047, and r= 0.441, P= 0.022) respectively, while each vitamin E and K were not significantly correlated with the score of the embryo on the 5th day. No significant correlations were found between the concentrations of all vitamins in follicular fluid and the embryo score on day 2 or 3 as illustrated in (Table 8).

Table 8: Correlation between vitamin concentrations in follicular fluid and the scores of embryo quality.

Vitamin level in follicular fluid	Embryo score day 2		Embryo score day 3		Embryo score day 5	
	Correlation	P- Value	Correlation	P- Value	Correlation	P- Value
Vitamin A	- 0.178	0.375	0.084	0.676	- 0.383	0.046
Vitamin D	- 0.012	0.939	0.036	0.921	- 0.441	0.022
Vitamin E	- 0.165	0.351	0.067	0.187	- 0.236	0.142
Vitamin K	- 0.043	0.792	0.036	0.873	- 0.253	0.149

Discussion

Infertility is a medical condition that affects both individuals and couples, leading to significant psychological, physical, and medical burdens [31]. Assisted reproductive technologies (ART), including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have revolutionized infertility management, with success rates of up to 50% in some studies [32]. The success of ART depends on embryo quality, and despite high fertilization rates, only a few embryos reach the blastocyst stage [33]. Recently, the assessment of fat-soluble vitamins in follicular fluid (FF) has emerged as a potential marker for oocyte quality and embryo development [34]. Studies have shown that vitamins A, D, and E influence fertility outcomes, with vitamin D playing a role in reducing inflammation and promoting fertility [35]. The concentration of vitamin K in FF has also been proposed as a novel marker of oocyte and embryo quality [36]. In this study, 60 infertile women undergoing ICSI were included. The mean age was 33.07 ± 5.24 years, with nearly half (48.3%) aged ≥35 years. Primary infertility was reported in 68.3%, and male factor infertility was the most common cause (31.7%). The most frequent duration of infertility was 5-9 years (41.7%), and 53.3% had a normal BMI. Comparative studies by Jeremic *et al*. and Yaseen *et al*. reported similar demographic trends but with variations in BMI and infertility duration [37, .38].

The pregnancy rate in this study was 33.3%, with top-quality embryos observed in 38.3% on day 2, 26.7% on day 3, and 16.7% on day 5. This aligns with Ciepiela *et al*., who reported a 39.6% pregnancy rate [34], while Yi H *et al*. observed a higher pregnancy failure rate of 49.7% [39]. Pregnancy failure was significantly associated with age ≥35 years, primary infertility, and infertility duration >10 years, consistent with studies by Yi H *et al*. and Wang *et al*. [39, 40]. However, Winter *et al*. found no significant effects of age, obesity, or other risk factors on ICSI outcomes [41]. Age-related ovarian decline and increased aneuploidy rates have been linked to reduced fertility and ART success [42]. In this study, lower anti-Müllerian hormone (AMH) levels were significantly associated with pregnancy failure (P=0.001). Alanazy *et al*. also reported lower pregnancy rates in ICSI cycles with low AMH levels [43]. Conversely, Yumen *et al*. found that pregnancy rates were lower in the high-AMH group [44], highlighting conflicting findings regarding AMH's predictive role in ART success. While AMH is a superior ovarian reserve marker compared to FSH and estradiol, its interpretation should be combined with other clinical factors [45]. A strong positive correlation was observed between serum and FF levels of vitamins A, D, E, and K (P=0.001). This aligns with Skowrońska *et al*. and Ciepiela *et al*., who reported significant serum-FF correlations [34, 46]. Vitamin D levels in FF have been linked to its systemic availability, though its impact on oocyte quality remains debated [47]. This study found significant associations between FF vitamin A and E levels and pregnancy success (P=0.002, P=0.026). Skowrońska *et al*. also found that vitamin A and E were predictors of fertilization success, while vitamin K showed no association [46]. In contrast, Alawad *et al*. reported a significant correlation between vitamin D and ICSI success [48], underscoring inconsistencies across studies. FF vitamin A was significantly associated with top-quality embryos on day 2 (P=0.001), but vitamins D, E, and K were not. This supports findings from Skowrońska *et al*., where vitamin A was linked to early embryo quality [46]. On day 3, vitamin A, D, and E levels correlated significantly with embryo development, with a continued effect on day 5 ($p<0.05$). Studies by Ciepiela *et al*. and Skowrońska *et al*. corroborate these findings, showing vitamin A and E's role in enhancing embryo development [34, 46]. However, some studies suggest that excessive FF vitamin D levels may negatively impact late-stage embryo development [46].

Conclusion

Combining standard morphological examination with follicular fluid vitamin analysis may help pick a better embryo for transfer, improving the chance of conception, and more accurately assess embryonic developmental capability.

Conflict of Interest

Not available

Financial Support

Not available

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