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Original article

Prognostic value of endometrial thickness in predicting pregnancy onset in IVF cycles: Insights from the "Ansagan Sabi" state program in Kazakhstan

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Abstract. *Background:* The introduction of the "Ansagan Sabi" program has expanded access to infertility treatment to patients in Kazakhstan. Endometrial thickness is a crucial factor in determining endometrial receptivity and, consequently, the success of in vitro fertilization (IVF) procedures. Our study seeks to assess the prognostic value of endometrial thickness as a predictor of pregnancy onset in patients undergoing fresh IVF cycles as part of the implementation of the "Ansagan Sabi" state program. *Methods:* A retrospective analysis was conducted on 279 women who underwent IVF fresh cycle procedures and were recruited under the "Ansagan Sabi" program. Strict selection criteria were applied during the outpatient stage. Demographic and clinical data, including endometrial thickness, were collected for analysis. *Results:* The analysis revealed that endometrial thickness significantly influenced the likelihood of pregnancy onset, as assessed by logistic regression analysis. Patients with endometrial thickness below 5 mm (Group 1) and between 5 and 7 mm (Group 2) exhibited decreased odds of pregnancy onset compared to those with thicknesses equal to or greater than 7 mm (Group 3). *Discussion:* Optimal endometrial thickness, indicated by thicknesses equal to or greater than 7 mm, was associated with improved pregnancy outcomes. The study findings have implications for patient management strategies within the "Ansagan Sabi" program and underscore the importance of optimizing endometrial conditions to enhance IVF success rates. Further research incorporating larger sample sizes and multicenter studies is warranted to validate the findings and explore additional prognostic factors. (www.actabiomedica.com)

Key words: endometrial thickness, IVF, pregnancy onset, prognostic value, "Ansagan Sabi" program

Introduction

Reproductive dysfunction presents a significant global challenge, impacting approximately one-sixth of couples during their reproductive years, as reported by the European Society of Human Reproduction and Embryology (ESHRE) (1). In Kazakhstan, the integration of Assisted Reproductive Technologies (ART) into mandatory social health insurance coverage, coupled with the implementation of the "Ansagan Sabi" State Program (2), has facilitated access to these procedures for numerous couples and expanded the pool of patients eligible for ART treatment (3). With stringent selection criteria detailed further in the methods section, the year 2021 witnessed a rise in patients with more favorable prognoses seeking

IVF treatment, thereby augmenting the success rates of IVF procedures. A recent review on neonatal outcomes and long-term follow-up of children born from frozen embryos shows that an increase in frozen embryo transfer (FET) has led to enhanced success rates in pregnancy and live births, along with a decreased risk of ovarian hyperstimulation syndrome and multiple pregnancies (4). Moreover, FET is associated with higher neonatal birth weights (5). An increased risk of minor congenital heart defects occurs in children conceived through ART, though these typically do not require surgical correction (6). Despite the overall advancements in IVF efficacy, implantation failure remains a significant hurdle in improving success rates. The capacity of the endometrium to facilitate normal implantation, termed receptivity, plays a pivotal role in ensuring successful pregnancies. Endometrial thickness and structure have emerged as major prognostic indicators of endometrial receptivity (7). Nevertheless, consensus regarding whether sonographic endometrial characteristics reliably predict pregnancy outcomes remains elusive (8). Decreased endometrial receptivity correlates with diminished pregnancy rates in ART programs, alongside increased incidences of miscarriages and ectopic pregnancies (4,5). Understanding the prognostic implications of endometrial thickness concerning pregnancy loss and ART inefficiency remains a critical focus in reproductive medicine (9). While endometrial thickness below 7 mm during the presumed "implantation window" offers minimal prospects for successful conception (10), instances of successful implantation with endometrial thicknesses as low as 4-6 mm challenge this notion, underscoring the complex nature of endometrial receptivity. In a systematic review and meta-analysis, the independent predictive ability and prognostic value of endometrial thickness for IVF-induced pregnancies were investigated. This analysis revealed significantly lower clinical pregnancy rates with endometrial thicknesses ≤ 7 mm compared to thicknesses exceeding 7 mm: 23.3% and 48.1%, respectively (11). In a recent systematic review of the literature on endometrial thickness and live birth rates after IVF, which demonstrated that risk factors play a major role in the predictive value of endometrial thickness for pregnancy onset and live birth rates (12). Despite extensive research on identifying factors associated with pregnancy loss, comprehensive studies are warranted to delineate and understand all prognostic risk factors and the predictive value of endometrial thickness (13). Our study seeks to assess the prognostic value of endometrial thickness as a predictor of pregnancy onset in patients undergoing fresh IVF cycles as part of the implementation of the "Ansagan Sabi" state program.

Methods

We conducted a retrospective analysis of 279 women who underwent IVF-ICSI fresh cycle procedures at the Scientific Center of Obstetrics, Gynecology, and Perinatology in Almaty, Kazakhstan, between January 1, 2021, and June 30, 2023. Patients were recruited under the "Ansagan Sabi" extension of the state Compulsory Social Medical Insurance program. Selection criteria during the outpatient stage included strict assessment of age, medical history, ovarian reserve and other risk factors presented in Table 1. All patients were selected to be part of the program based on the evaluation of all selection criteria to ensure uniformity (2).

For this analysis, demographic and patient characteristic data were collected, including age, body mass index (BMI), duration and type of infertility, outcomes of previous pregnancies, history of reproductive losses, gynecological diseases, endometrial thickness, and levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and anti-Müllerian hormone (AMH).

Outcome variables

The outcome variable of this study is the onset of clinical pregnancy which was defined as a pregnancy with a positive result subsequently confirmed by ultrasound.

Ultrasound examinations

All ultrasound examinations were performed by specialist physicians following standardized protocols, utilizing Voluson E10 ultrasound machines in the department. Endometrial thickness and pattern were assessed in the mid-sagittal plane of the uterine body on the day of human chorionic gonadotropin (hCG) administration. The maximum thickness was measured

Table 1. Criteria for inclusion in the program**.**

Variable name	Selection criteria
Age (years)	18-42
AMH ng/mL	>1.0
FSH (on 2-5 day of cycle) mIU/mL	<12
Antral follicle count in each ovarium (on the 2-5 day of cycle)	≥3
Antral follicle count in the ovarium if there is only one (on the 2-5 day of cycle)	5-6
Absence of the following risk factors that reduce the pregnancy onset	• developmental anomalies of internal reproductive organs that hinder the implantation or pregnancy development • hydrosalpinx • advanced uterine cavity adhesions • ovarian cysts • non-obstructive azoospermia
Infertility caused by the following male factors	• oligozoospermia • asthenozoospermia • teratozoospermia • combined sperm pathology • presence of antisperm antibodies in ejaculate

Abbreviations: AMH: Anti-Müllerian Hormone; FSH: Follicle-Stimulating Hormone

from one border of the endometrium-myometrium junction to the other. For the present analysis, patients were categorized into three groups based on endometrial thickness: Group 1 (>5 mm), Group 2 (≥5 and <7 mm), and Group 3 (<7 mm).

Statistical analysis

Statistical analysis was conducted utilizing the SPSS software package, version 21 (14). Continuous data are expressed as means and standard deviations, while categorical data are presented as frequencies and percentages. The threshold for statistical significance was set at a p-value < 0.05. A chi-square test was employed to examine differences between the endometrial thickness groups. Additionally, to evaluate the predictive value of endometrial thickness on pregnancy onset, we conducted a univariate binary logistic regression analysis.

Results

A total of 279 medical records of patients who underwent IVF with fresh embryo transfer were retrospectively analyzed. All patients underwent the intracytoplasmic sperm injection (ICSI) procedure as well. Among these, 222 (79.6%) followed short treatment protocols, while 57 (20.4%) followed long treatment protocols. The age of the participants ranged from 19 to 42 years, with a mean age of 32.94 ± 4.9 years (mean ± SD). The mean BMI was 24.18 ± 4.4. The duration of infertility varied from 1 to 20 years, with an average duration of 6.54 ± 3.9 years. Noteworthy indicators from the medical histories included reproductive losses, such as spontaneous abortions (66 cases, 23.7%), ectopic pregnancies (64 cases, 22.9%), and previous ineffectiveness of IVF programs (23 cases, 8.2%). Hormonal profiles revealed average serum levels of AMH of 3.2 ± 3 ng/mL, LH at 6.36 ± 4.3 IU/L, and FSH at 7.14 ± 5.6 mIU/mL. Table 2 summarizes the characteristics of the patients.

Endometrial thickness

On the day of hCG administration, the endometrial thickness ranged from 3 to 18 mm. Among all participants, the mean endometrial thickness (±SD) was 6.2 ± 2.5. Analysis of groups based on endometrial thickness revealed: 25.1% of the patients were in Group 1, 43.0% of the patients were in Group 2, and

Table 2. Characteristics of Patients Undergoing IVF-ICSI with Fresh Embryo Transfer: Demographic and Clinical Profile.

Variable	Mean±SD, or number (%)
Treatment protocol	
Short	222 (79.6%)
Long	57 (20.4%)
Age, years	32.94 (4.9)
	Range (19-42)
BMI	24.18±4.4
Residence	
Urban	133 (47.7)
Rural	146 (52.3)
Social Status	
Employed	101 (36.2)
Unemployed	175 (62.7)
Self-employed	2 (0.7)
Duration of infertility, years	6.54±3.9
	Range (1-20)
Previous pregnancies[1]	
0	116 (41.6)
1	72 (25.8)
2	31 (11.1)
3	33 (11.8)
4	17 (6.1)
5	2 (0.7)
Previous delivery[1]	
0	183 (65.6)
1	60 (21.5)
2	17 (6.1)
3	5 (1.8)
Diagnosis of infertility	
Yes	119 (42.7)
No	160 (57.3)
First trimester miscarriage	
Yes	66 (23.7)
No	213 (76.3)
Ectopic pregnancy	
Yes	64 (22.9)
No	215 (77.1)
Unsuccessful IVF history	
Yes	23 (8.2)
No	256 (91.8)
Male factor	
Yes	145 (52.0)
No	134 (48.0)
Tubal factor	
Yes	207 (74.2)
No	72 (25.8)
Endometriosis	
Yes	33 (11.8)
No	246 (88.2)
Chronic endometritis	
Yes	51 (18.3)
No	228 (81.7)
Endocrine factors[1]	
Yes	22 (7.9)
No	254 (91.0)
Unspecified [1]	
Yes	9 (3.2)
No	268 (96.1)
Endometrial thickness, mm	
>5	70 (25.1)
5-7	120 (43.0)
<7	89 (31.9)
Mean (SD)	6.21 ± 2.5
AMH ng/mL	3.20±3.0
LG IU/L	6.36±4.3
FSH (on 2-5 day of cycle) mIU/mL	7.14±5.6

[1] percentages do not add up to 100 due to missing values.
Abbreviations: AMH: Anti-Müllerian Hormone; BMI: Body mass index; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; SD: standard deviation.

31.9% of the patients were in Group 3. The overall distribution of endometrial thickness frequencies (mm) is presented in Figure 1.

Table 3 presents the odds ratios (OR) derived from logistic regression analysis assessing the impact of endometrial thickness groups on the onset of pregnancy. Being in Group 1 was associated with decreased odds of pregnancy onset (OR=0.595, 95% CI [0.524-0.676]) compared to those who were Group 3. Being in Group 2 was associated with decreased odds of pregnancy onset (OR=0.670, 95% CI [0.591-0.761]) compared to those who were Group 3. The outcomes of the univariate logistic regression analysis, investigating the predictive value of additional demographic and clinical variables on pregnancy onset, can be found in Supplementary Table (S1 Table). Those associations were not significant.

Discussion

The present study aimed to investigate the association between endometrial thickness and the onset

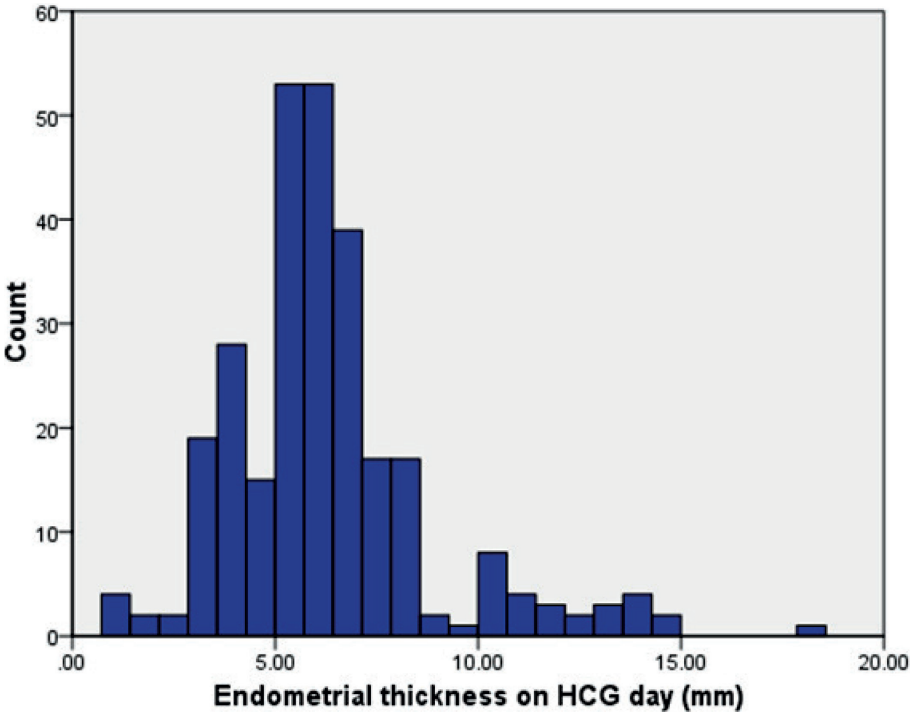

Figure 1. The frequency distribution of the endometrial thickness on HCG day: 25th percentile: 4.9 mm; 50th percentile: 6.0 mm; 75th percentile: 7.0 mm.

Table 3. Odds Ratios for the effect of endometrial thickness on the onset of pregnancy from logistic regression analysis.

Variable	OR	95% CI	p-value
Endometrial Thickness Groups (Reference: Group 3)			
Group 1	0.595	0.524-0.676	<0.001
Group 2	0.670	0.591-0.761	<0.001

Abbreviations: CI: confidence interval; OR: odds ratio

of clinical pregnancy in women undergoing IVF-ICSI fresh cycle procedures who were preselected for the procedure to minimize the pregnancy onset and loss risk factors. In our retrospective analysis of 279 women undergoing IVF-ICSI, we observed that endometrial thickness significantly influenced the likelihood of pregnancy onset. The results of the logistic regression analysis showed that among the multitude of factors influencing the onset of pregnancy, endometrial thickness consistently emerges as one of the most important factors. Patients in Group 1 and in Group 2, exhibited decreased odds of pregnancy onset compared to those in Group 3, whose endometrial thickness on hCG day was equal or greater than 7 mm. These findings suggest that optimal endometrial thickness, as indicated by Group 3, may be associated with improved pregnancy outcomes in IVF-ICSI procedures.

Our results are consistent with previous research highlighting the importance of endometrial thickness in predicting IVF success. According to the meta-analysis results, the pooled pregnancy rate in women with endometrial thickness of 7 mm or less was 23.3% and was significantly lower than in patients with endometrial thickness of greater than 7 mm (11). Adequate endometrial thickness is crucial for successful implantation and embryo development. The observed association between endometrial thickness and pregnancy onset underscores the need for meticulous monitoring and optimization of endometrial conditions during IVF-ICSI cycles.

Our analysis explored various demographic and clinical factors potentially influencing pregnancy outcomes in pre-selected patients. While some of these factors may independently affect pregnancy outcomes,

we did not find any significant associations which could be due to the small number of sample size. We also did not include thyroid autoimmunity (TAI) to the clinical factors that were analyzed. TAI is identified as a significant cause of female infertility, associated with decreased ovarian reserve and potential hindrances in oocyte maturation and embryo development, ultimately affecting pregnancy outcomes (15). Another limitation is the generalizability of our study findings. This is a single center study that focused on the pregnancy onset of the patients that were preselected, which may limit the generalizability of our results. As a retrospective analysis, our findings are subject to inherent biases and confounding variables. Future research incorporating larger sample sizes and multicenter studies is warranted to validate our findings and provide further insights into the role of endometrial thickness in IVF-ICSI outcomes.

It is important to mention, despite the fact that it is outside the scope of the present study, that fertility preservation strategies, such as oocyte vitrification, are becoming increasingly important for women who are seeking fertility sparing treatments in order to preserve their reproductive potential (16). The vitrification of oocytes offers women the opportunity to secure future reproductive options, especially if they are undergoing IVF-ICSI at an advanced age or have preexisting fertility issues, allowing for a non-invasive prenatal diagnosis test and monitoring of neonatal outcomes (17). Including oocyte vitrification in government-funded programs, such as "Ansagan Sabi," which facilitate access to ART, could potentially improve IVF success rates.

Our findings could serve as valuable insights for the evaluation of the "Ansagan Sabi" program effectiveness. During the first two years of program implementation, IVF was performed for over 19,000 women, resulting in pregnancy for over 7,000 women (18). By incorporating endometrial thickness as a key predictor of pregnancy outcomes in pre-selected patients undergoing IVF-ICSI procedures, the program can enhance its effectiveness in minimizing pregnancy onset and loss risk factors. Specifically, the program can utilize our findings to optimize patient selection criteria, refine treatment protocols, and improve monitoring strategies to ensure optimal endometrial conditions during IVF-ICSI cycles.

Conclusions

In conclusion, our study demonstrates that endometrial thickness is a significant predictor of pregnancy onset in women undergoing IVF-ICSI procedures. Optimal endometrial thickness, as indicated by <7 mm, is associated with improved pregnancy outcomes. Clinicians should consider monitoring and optimizing endometrial conditions to enhance the success rates of IVF-ICSI cycles. Further research is needed to confirm our findings and explore additional factors influencing IVF-ICSI outcomes.

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Human and Animal Rights: This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Ethical Statement: This study was approved by the Local Ethics Committee of Kazakhstan Medical University "KSPH" (study ID: IRB-A289/1; date: 08/11/2023) with the exemption of informed consent. This study was approved by the Local Ethics Committee of Al-Farabi Kazakh National University (IRB00010790; date: 29/12/2022) with the exemption of informed consent.

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Availability of Data: Data of this study is available upon request.

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Appendix

Supplementary file

S1 Table. Odds Ratios for the effect of endometrial thickness on the onset of pregnancy from logistic regression analysis.

Variable	OR	95% CI	p-value
Age	0.998	0.987-1.009	0.747
Duration of infertility. years	0.983	0.923-1.046	0.589
Previous Pregnancy	1.004	0.830-1.214	0.970
Delivery	1.087	0.762-1.552	0.644
BMI	0.994	0.980-1.007	0.356
AMH	0.990	0.977-1.004	0.172
LH	1.003	0.989-1.016	0.700
FSH	0.922	0.848-1.002	0.056
Infertility	1.031	0.920-1.154	0.602
First trimester miscarriage	1.579	0.867-2.877	0.135
Ectopic pregnancy	1.356	0.747-2.461	0.316
Unsuccessful IVF	1.088	0.445-2.662	0.854
Male factor	0.831	0.510-1.354	0.457
Tubal factor	0.898	0.512-1.574	0.707
Endometriosis	0.571	0.275-1.187	0.133
Endocrine genesis	2.734	0.899-8.319	0.076
Unspecified	0.439	0.115-1.675	0.228
Place of Residence (Reference: rural)			
Urban residence	0.673	0.413-1.098	0.113
Social Status (Reference: self-employed)			
Employed	1.658	0.101-27.288	0.724
Unemployed	0.933	0.562-1.549	0.787