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IVF PREGNANCY DATING: COMPARATIVE ANALYSIS OF GESTATIONAL AGE ESTIMATION BASED ON EMBRYO TRANSFER DATE AND ULTRASOUND MEASUREMENTS OF CROWN-RUMP LENGTH

DATIRANJE TRUDNOĆE VANTELESNO REALIZOVANE – UPOREDNA ANALIZA PROCENE GESTACIJSKE STAROSTI NA OSNOVU DATUMA EMBRIOTRANSFERA I ULTRAZVUČNOG MERENJA DUŽINE TEME–TRTICA

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Summary

Introduction. In in-vitro fertilization pregnancies, the precise date of conception is known. Relying solely on the embryo transfer date for pregnancy dating can lead to inaccuracies and mismanagement in prenatal care. This study aimed to compare gestational age estimated by first-trimester ultrasound measurements with gestational age determined by the known date of embryo transfer. **Material and Methods.** This retrospective study included 30 patients who conceived through in-vitro fertilization. Only patients with singleton pregnancies who underwent first-trimester ultrasound screening by a single sonographer between January 2008 and March 2024 were included. Gestational age was calculated for each patient based on ultrasound measurements of crown-rump length and the date of embryo transfer. **Results.** Gestational age estimated by ultrasound in our study was statistically significantly higher than that determined by the embryo transfer date. The mean difference was 0.9 days (±2.14, 95% confidence interval [0.1, 1.7]) ($p<0.05$), and a median difference was 0.5 days (interquartile range 0-2.75) ($p<0.05$). **Conclusion.** Gestational age estimated by crown-rump length was higher than that calculated by the known date of conception. For pregnancies conceived through in-vitro fertilization, it is advisable to consider both the date of embryo transfer and the gestational age calculated from ultrasound measurements for more accurate pregnancy dating.

Key words: Fertilization in Vitro; Gestational Age; Crown-Rump Length; Ultrasonography; Predictive Value of Tests; Embryo Transfer; Pregnancy Trimester, First

Sažetak

Uvod. U trudnoćama začetim vantelesnom oplodnjom, tačan datum začeća je poznat. Datiranje trudnoća samo na osnovu poznatog datuma embriotransfera potencijalno može dovesti do greške u proceni, te neadekvatnog postupanja u prenatalnom periodu. Naša studija je imala za cilj da uporedi gestacijsku starost procenjenu ultrazvučnim merenjima u prvom trimestru sa onom utvrđenom na osnovu poznatog datuma embriotransfera. **Materijal i metode.** Retrospektivnom studijom obuhvaćeno je 30 pacijentkinja koje su zatrudnele vantelesnom oplodnjom. Uključili smo samo pacijentkinje sa jednoplodnim trudnoćama koje je ultrazvučno pratio isti sonograf u periodu od januara 2008. do marta 2024. Za svaku pacijentkinju, gestacijska starost je izračunata na osnovu ultrazvučnog merenja dužine teme–trtica i datuma embriotransfera. **Rezultati.** Gestacijska starost procenjena ultrazvukom u našoj studiji bila je značajno viša, sa prosečnom razlikom od 0,9 dana (± 2,14, 95% interval poverenja [0,1, 1,7]) ($p < 0,05$) i srednjom razlikom od 0,5 dana (interkvartilni opseg 0–2,75) ($p < 0,05$). **Zaključak.** Gestacijska starost procenjena na osnovu dužine teme-trtica bila je viša u našoj studiji. Pored datiranja trudnoća dobijenih u vantelesnoj oplodnji na osnovu poznatog datuma začeća, bilo bi dobro uzeti u obzir i vrednost dobijenu ultrazvučnim merenjima radi veće preciznosti.

Ključne reči: vantelesna oplodnja; gestacijska starost; dužina teme-trtica; ultrasonografija; prediktivna vrednost testova; embriotransfer; prvi trimestar trudnoće

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Introduction

Gestational age (GA) is defined as the time elapsed from the first day of the last menstrual period to the current date. It is a critical parameter used by obstetricians to manage pregnancies and assess fetal growth and development.

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Abbreviations

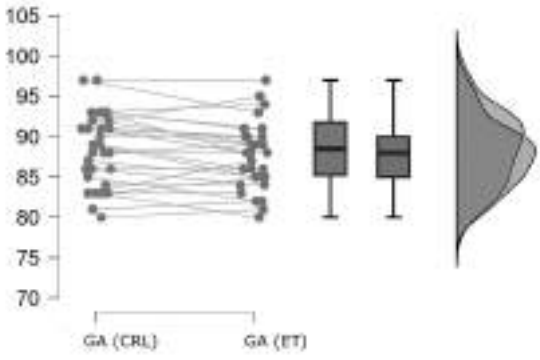
GA – gestational age
IVF – in vitro fertilization
ET – embryo transfer
CRL – crown-rump length
FMF – Fetal Medicine Foundation
IQR – interquartile range
BMI – body mass index

Accurate determination of GA is essential in obstetrics, as errors can impact both maternal and fetal health outcomes. GA is vital for the timing of various prenatal interventions, such as labor induction and corticosteroid therapy administration, and it is crucial in managing pregnancies with small-for-gestation age fetuses [1].

Throughout history, several methods have been employed to estimate GA, ranging from menstrual history-based calculations to advanced ultrasound measurements. Each method has its limitations, and accurate GA estimation remains a challenge for obstetricians worldwide [1].

In the context of in vitro fertilization (IVF), the absence of natural menstrual cycle means that conventional GA estimation methods may not be directly applicable. GA in IVF pregnancies can be determined using various milestones within the IVF procedure [2].

The most common method involves dating the pregnancy from the date of embryo transfer (ET), which is the introduction of the fertilized embryo(s) into the uterine cavity. The date of the oocyte retrieval is considered the date of conception. Depending on the stage of embryo development (cleavage-stage embryo or blastocyst), the ET date serves as the starting point for pregnancy dating in IVF cycles. In frozen IVF cycles, the stage of embryo development at cryopreservation and the dates of embryo thawing and transfer, are considered. GA may also be calculated from the date of embryo biopsy in cases of pre-implantation genetic testing. These methods are generally reliable and widely used [2, 3].



Graph 1. Comparison between gestational age estimated by crown-rump length in the first trimester and by the known date of embryo transfer.

Grafikon 1. *Poređenje gestacijske starosti određene na osnovu dužine teme–trtica i poznatog datuma embriotransfera*

*GA (CRL) – gestational age estimated by crown-rump length/*gestacijska starost određena na osnovu dužine teme-trtica*

*GA (ET) – gestational age estimated by the known date of embryo transfer/*gestacijska starost određena na osnovu poznatog datuma embriotransfera*

However, dating pregnancies solely by the known date of embryo can lead to inaccuracies and mismanagement of prenatal care due to variations in embryo development and implantation timing. Embryos transferred during IVF cycles may develop at different rates compared to those in natural cycles, causing discrepancies between the actual age of the embryo and the calculated GA [4]. Factors such as embryo quality, uterine cavity conditions, and maternal hormonal settings in IVF cycles can further influence embryo development and implantation timing [5, 6].

First-trimester ultrasound dating provides direct visualization of the embryo and allows precise measurement of the gestational sac size and crown-rump length (CRL). This method can minimize the uncertainties associated with embryo transfer dating [7].

The aim of this study was to compare GA estimated by first-trimester ultrasound measurements with GA determined by the known date of ET. The goal is to enhance the understanding of GA determination in IVF pregnancies and support improvements in prenatal care practices.

Material and Methods

This retrospective study was conducted at the Clinic of Gynecology and Obstetrics, University Clinical Center of Vojvodina, covering the period from January 2008 to March 2024. The study received approval from the ethical committee of the University Clinical Center of Vojvodina.

Data including maternal age, weight, height, smoking status, ultrasound findings, date of ultrasound examination, and date and time of embryo transfer were collected anonymously and retrospectively from patients' medical records, eliminating the need for informed consent from the patients.

We enrolled 30 patients who conceived pregnancies through conventional IVF at our department, including both fresh and frozen IVF cycles. Pregnancies achieved by intracytoplasmic sperm injection were excluded. Only singleton pregnancies were considered, and multifetal pregnancies were excluded. Additionally, patients with first-trimester screening results indicating an increased risk for genetic anomalies were excluded, as genetic anomalies can affect fetal growth rates, as observed in fetuses with trisomy 18 and triploidy [8].

All patients underwent first-trimester screening for chromosomal abnormalities in accordance with the Fetal Medicine Foundation (FMF) guidelines [9]. All ultrasound examinations were performed by the single experienced and FMF-certified sonographer.

For each patient, gestational age (GA) was calculated based on ultrasound measurements and the date of embryo transfer.

The crown-rump length (CRL) of each fetus was used as the ultrasound parameter. This measurement was taken using a transabdominal beam, and in some cases, a transvaginal beam when necessary. The fetus was positioned horizontally so that the line from crown to rump is approximately 90° to the ultrasound beam, and assessed in a neutral position without hyperflexion or hyperextension. The image was zoomed to fill most of the screen, and calipers were placed on the endpoints of the crown and rump. GA calculations were based on the highest quality measurement between 45 and 84 mm [9]. The formula developed by Robinson and Fleming was then used to calculate GA from CRL: GA (weeks) = 8.052 × CRL (cm) + 23.73 [10].

GA was calculated for each patient from known conception dates using the following steps: for fresh cycles, the date of oocyte retrieval was set as the date of conception; in frozen-thawed cycles, conception was dated as 4 days prior to cleavage stage embryo transfer or 6 days before blastocyst transfer [11].

The Shapiro-Wilk test was initially conducted to verify the normality of the data distribution. Descriptive statistical methods used included mean ± SD, median, and interquartile range (IQR). Additional descriptive statistics, such as frequencies and percentages, were also employed. Comparisons were made using both the Student's t-test for paired samples and the Wilcoxon signed-rank test. P values less than 0.05 were considered statistically significant. Data was visually represented using tables and graphs. Statistical analysis was conducted using the open-source statistical software JASP (JASP Team, 2024, Version 0.18.3, Amsterdam, Netherlands).

Results

The median age of the women at the beginning of pregnancy was 33.5 years (IQR 31-36). The median height was 168.5 cm, and the median weight was 63.5 kg (IQR 165-172; 59.25-71, respectively). The median BMI was 23.5 (IQR 21.8-24.6). Only two patients (6.67%) had a body mass index (BMI) over 25, while the remaining 28 patients (93.33%) were within the normal weight range.

Three patients (10%) were smokers.

The Shapiro-Wilk test confirmed that the data representing GA estimated by CRL and by the known date of ET followed a normal distribution. Therefore, a paired samples t-test was performed to compare the two methods, which showed statistical significance (t=2.304; p=0.029). A non-parametric Wilcoxon signed-rank test was also indicated statistical significance (t=194; p=0.028).

The mean value of GA estimated by CRL was 88.43 days (±4.48 95% CI [86.76, 90.10]). The mean value of GA estimated by the known date of ET was 87.53 days (±4.15 95% CI [85.98, 89.08]). The median GA values were 88.5 days (IQR 85.25–91.75) and 88 days (IQR 85–90), respectively. GA estimated by ultrasound was higher than GA estimated by the known date of ET, with a mean difference of 0.9 days (±2.14, 95% CI [0.1, 1.7]) ($p<0.001$) and a median difference of 0.5 days [0-2.75] ($p<0.001$). The median GA values were 88.5 days (IQR 85.25–91.75) and 88 days (IQR 85–90), respectively ($p<0.001$). GA estimated by ultrasound was higher than GA estimated by the known date of ET, with a mean difference of 0.9 days (±2.14, 95% CI [0.1, 1.7]) and a median difference of 0.5 days [0-2.75]. In a sample of 30 patients, three (10%) showed a four-day difference in gestational age when assessed by the two methods, and six (20%) showed a three-day difference. **Figure 1** illustrates the comparison between GA estimated by ultrasound measurements in the first trimester and by the known date of ET.

Of all the pregnancies studied, 23 (77%) were obtained through fresh embryo transfer, and the remaining 7 pregnancies (23%) were obtained through frozen embryo transfer.

Discussion

The median age of the women at the beginning of pregnancy was 33.5 years (IQR 31-36), which falls within the typical childbearing age range. The median height of the women in our study was 168.5 cm (IQR 165-172), median weight was 63.5 kg (IQR 59.25-71), and the median BMI was 23.5 (IQR 21.25-24.6). Only two patients were overweight, with a BMI exceeding 25, and there were no obese patients, indicating that our sample generally consisted of women within the healthy weight range according to WHO classifications [12].

In our study sample, only 3 patients (10%) were smokers. Maternal smoking during pregnancy has been shown to impact embryo development early in the first trimester, potentially leading to delayed or altered development [13].

Given the small sample size, we conducted not only a t-test for paired samples but also sensitivity analyses using a non-parametric Wilcoxon signed-rank test to determine if there was a difference between GA calculated by ultrasound and by the known date of ET. Consistent with the findings of the paired samples t-test, the Wilcoxon signed-rank test also showed a statistically significant difference between the two methods of GA estimation. This underscored the robustness of our conclusion regarding the observed difference.

GA estimated by ultrasound in our study was significantly higher, with a mean difference of 0.9 days (±2.14, 95% CI [0.1, 1.7]) and a median difference of 0.5 days (IQR 0-2.75). Our findings were consistent with those of Rapisarda et al. [11], who reported a median difference of 1 day (IQR 0-2), with ultrasound GA being significantly higher than GA calculated by the known date of ET. Bonne et al. showed similar results, with a median difference of 2.3 days (SD 2.36 days), indicating that GA estimated by ultrasound resulted in higher values [14]. Knight et al. noted a mean difference of 3 days (95% CI [2.7, 3.36]), demonstrating that the ultrasound dating method reported higher values [15].

Currently, there is no clear scientific consensus on why ultrasound-estimated GA may be higher, but several hypotheses exist. The selection and culture of embryos in a lab environment may accelerate early embryonic development, leading to greater ultrasound measurement values [16]. Additionally, hormonal treatments used in IVF cycles may influence embryonic growth rates [17]. It has been shown that early implantation of an embryo leads to a larger CRL [18], which may also explain the observed difference, but further research regarding ovulation and implantation timing is needed.

On the other hand, some studies provide evidence suggesting there are no differences in embryonic growth trajectories between naturally conceived and IVF pregnancies [19, 20].

Our findings showed that patients exhibited differences of three days (6 patients, 20%) and even four days (3 patients, 10%) in GA when assessed by two methods used in our study. This variability should not be overlooked, as it is common enough to potentially lead to incorrect decisions in obstetrics. Inaccurate GA can result in either premature or delayed interventions. Precise GA estimation is crucial, particularly when considering assessments for small for gestational age, timing of labor induction, and administration of corticosteroid therapy [1, 21–24]. This is especially important in IVF pregnancies, which are associated with higher risks compared to spontaneously conceived pregnancies [25, 26].

According to ISUOG practice guidelines, CRL measured by ultrasound should be used for GA estimation in all cases except pregnancies conceived by IVF [8]. However, it would be prudent to also consider the date obtained through CRL measurements for additional accuracy.

Conclusion

The gestational age estimated by ultrasound is significantly higher than the gestational age based on the date of embryo transfer.

When dating IVF pregnancies, it would be prudent to consider not only the gestational age based on the date of embryo transfer but also the gestational age obtained through CRL measurements for additional accuracy.

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