

Heart Activity Visualization in Embryos with Crown-Rump Length Shorter Than 5 mm and Its Role in Prediction of Early Pregnancy Failure in Patients of Recurrent Early Pregnancy Loss

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ABSTRACT

Background: Previously, only embryos with a crown-rump length (CRL) of ≥ 5 mm could have their heart activity seen using ultrasonography. However, due to advancements in ultrasound resolution, viable embryos with CRL as small as 2 mm may now be diagnosed. **Objective:** The current study aimed to investigate whether early embryonic heart rate (EHR) in embryos with smaller CRL may be used as a predictor of pregnancy outcome.

Methods: This prospective cohort study included 78 cases, from June 2023 to May 2024. All women had a history of recurrent pregnancy. Early transvaginal ultrasound was done with EHR and was assessed using M-mode. Follow-up was done to determine the outcome of the pregnancy after 12 weeks. The negative outcome manifested as a spontaneous pregnancy loss that transpired at or prior to 12 weeks of gestation.

Results: A normal CRL diameter was present in 79.6% of the CRL in the examined groups. With cases of normal diameter that ended in miscarriage, only one had a CRL that lasted past the first trimester. With a total accuracy of 99.1%, CRL's sensitivity and specificity for miscarriage prediction were 98.6% and 100%, respectively. With a total accuracy of 98.1%, When anticipating a first-trimester pregnancy outcome, EHR's overall accuracy was 98.2%, with specificity of 100% and sensitivity of 97.4%. **Conclusion:** These days, most embryos with a CRL of 2 to 5 mm can show cardiac activity. About 80% of the time, non-visualization at this point is linked to embryonic death. A poor pregnancy outcome is linked to both embryonic bradycardia and small CRL.

Keywords: Crown-Rump Length, Embryonic Heart Rate, Recurrent Pregnancy Loss.

INTRODUCTION

According to the classification provided by the World Health Organization (WHO), the occurrence of three or more consecutive pregnancy losses prior to the 20th week of gestation is defined as recurrent miscarriage (RM)⁽¹⁾.

Previously, only embryos with a CRL measuring 5 mm or greater could have their heart activity seen using ultrasonography. Non-visualization of cardiac activity was considered normal when CRL was less than 5 mm. Nevertheless, improvements in ultrasonography resolution have enabled the detection of cardiac activity in embryos with a CRL as small as 2 mm⁽²⁾.

Since the first trimester is seeing an increase in the use of vaginal sonography, we may now measure the embryonic heart rate by observing embryonic cardiac activity during the sixth postmenstrual week⁽³⁾. A sluggish fetal heart rate (FHR) at a CRL of 5 mm or less has been linked to future fetal death, according to a few consistent findings. A single report of an unusually low heart rate does not always portend the later loss of an embryo but a persistent drop in EHR activity may unavoidably be linked to miscarriage⁽⁴⁾. An embryonic heart rate falling below 100 beats per minute is regarded as atypical and is associated with 83.3% of pregnancy losses. Consequently, evidence suggests a markedly increased risk of fetal demise when the heart rate is reduced at the early developmental phase, specifically at a CRL of 5 mm⁽⁵⁾.

The embryonic heartbeat can often be distinguished with greater visual clarity as early as five weeks. Motion mode (M-mode) and Doppler investigations are useful⁽⁶⁾.

AIM OF WORK

Improving fetal outcome by examining early embryonic heart rate (FHR) in embryos with a crown-rump length (CRL) of 5 mm or less in Patients with Recurrent Early Pregnancy Loss.

PATIENTS AND METHODS

This prospective cohort study involved 78 participants, from June 2023 to May 2024, all of whom had a history of recurrent pregnancy loss within the first trimester, between 6 weeks and 12 weeks + 6 days. Each case included a singleton pregnancy with an embryo exhibiting positive cardiac activity. Exclusion criteria included women with anembryonic pregnancies, absent embryonic cardiac activity, a history of threatened abortions, or any uterine pathologies such as myomas or malformations. Additionally, women with chronic conditions like systemic lupus erythematosus (SLE), hypertension, diabetes, or cardiac diseases were excluded.

A thorough medical history and comprehensive physical examination were performed on each patient. A transabdominal or transvaginal ultrasound was conducted to confirm intrauterine pregnancy and assess for uterine wall abnormalities. Gestational age, crown-rump length (CRL), and embryonic heart rate (EHR) were measured

using M-mode sonography through transvaginal ultrasound (TVS). The EHR was calculated by measuring the interval between two consecutive cardiac cycles following the recording of 6-10 heartbeats. A follow-up assessment was conducted at 12 weeks to determine pregnancy outcomes, either through an ultrasound examination or via a phone interview. The adverse outcome was defined as a spontaneous pregnancy loss occurring on or before the 12th week of gestation.

Ethical considerations:
The study protocol was approved by Zagazig University Institutional Review Board (IRB). Written informed consent was obtained from patients. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis:
All data were collected, tabulated, and statistically analyzed using SPSS version 20. Continuous Quantitative variables were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using the Shapiro-Wilk test. Categorical data were compared using the Chi-square test. P-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS). ROC curve: a receiver operating characteristic (ROC), or simply ROC curve, is a graphical plot that illustrates the performance of a binary classifier system as its discrimination threshold is varied. It is created by plotting the fraction of true positives out of the positives (TPR = true positive rate) vs. the fraction of false positives out of the negatives (FPR = false positive rate), at various threshold settings. TPR is also known as sensitivity (recall in some fields), and FPR is one minus the specificity or true negative rate.

RESULTS

The study included 78 cases. Table (1) displays the average age, BMI, and number of prior abortions for the patients in the current study. It also shows that 68% of the patients had more than three abortions.

Table (1): The studied group's demographics (n = 78)

Age (years)	25.8 ± 3.1
BMI (kgm ²)	25.4 ± 2.4
No. of previous Pregnancy losses	3 ± 0.7
Gravidity < 3	25 (32%)
> 3	53 (68%)
Parity 0	40 (51.2%)
>1	38 (48.8%)

Data are presented as mean ± standard deviation (SD) or as frequency and percentage.

The ultrasound results of the case under study showed that the EHR (b/m) was 129.5± 21, and the CRL (mm) was 5± 5.6. as shown in Table (2). Of those surveyed, 23.1% had an abortion (Table 3).

Table (2): Ultrasound findings (n = 78). Data are presented as Mean ± SD and range

CRL (mm)	5 ± 5.6 9-15
GS diameter (mm)	45 ± 13.7 26-61
Weeks of gestations	9.9 ± 1.6 6-12
Embryonic heart rate (EHR) (b/m)	129.5±21 (95-150)
YSD (mm)	39 ± 10.6 16-62

Table (3): Abortion distribution among the studied group (n = 78)

		N	%
Abortion	Not Aborted	60	76.9
	Aborted	18	23.1
	Total	78	100.0

A normal CRL diameter was present in 79.6% of the CRL in the examined groups (Table 4).

Table (4): Distribution of crown-rump length (CRL) (n = 78)

CRL	Frequency	%
Normal	62	79.6
Large	8	10.2
Small	8	10.2
Total	78	100

Just one instance of a normal diameter miscarriage occurred out of all the normal CRLs that lasted past the first trimester (Table 5).

Table (5): CRL's correlation with first-trimester results (n = 78)

CRL	Abortion	Continued beyond 12 weeks	Total	P-value
Normal	1	60	61	*<0.001
Large	5	0	5	
Small	12	0	12	
Total	18	60	78	

*: Significant

Regarding miscarriage prediction, CRL demonstrated a 98.6% sensitivity and 100% specificity, yielding a 99.1% overall accuracy (Table 6).

Table (6): Validity of CRL in first-trimester pregnancy outcome prediction (n = 78)

	CRL		Sensitivity	Specificity	PPV	NPV	Accuracy
	Normal	Abnormal					
Continue pregnancy	60	0	98.6%	100%	100%	91.9	99.1%
Miscarriage	1	17					

The sensitivity and specificity of the EHR for predicting first-trimester pregnancy outcomes were found to be 97.4% and 100%, respectively, resulting in an overall accuracy rate of 98.2% (Figure 1).

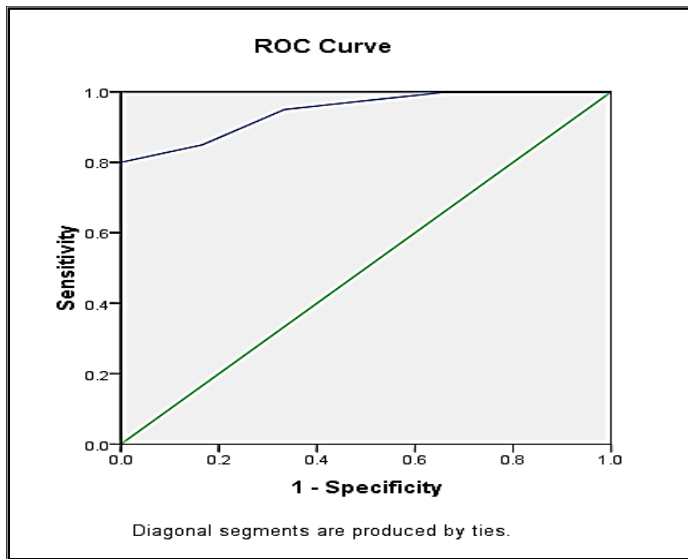


Fig. (1): The EHR's ROC curve for miscarriage prediction.

DISCUSSION

The WHO characterizes recurrent miscarriage (RM) as the loss of three or more consecutive pregnancies occurring before the completion of the 20th week of gestation ⁽¹⁾. Additionally, 1% of couples trying to conceive experience three or more losses, while 5% experience two miscarriages ⁽⁷⁾.

It has been reported that spontaneous pregnancy losses predominantly occur during the first trimester, with an estimated incidence of 30% to 40%. However, once embryonic cardiac activity is detected, the probability of spontaneous abortion significantly drops to approximately 2-5% ⁽⁸⁾. Research has shown that cardiac activity can be detected in most embryos with a CRL of 2 to 5 mm ⁽⁹⁾.

This study seeks to determine whether early embryonic heart rate (EHR) in embryos with a CRL of 5 mm or less can serve as a predictor of pregnancy outcomes in cases with a history of early recurrent miscarriages (RM).

We found that 68% of patients had more than three abortions. The study's sample size ranged from 3 to 5

abortions, with a mean of 3 ± 0.7. These have a resemblance to the findings documented by **Carp and colleagues** ⁽¹⁰⁾.

Falco et al. ⁽¹¹⁾ examined the correlation between sonographic results and abortion rates in two groups: one that underwent a threatened abortion and one that ended the pregnancy with both fetal heartbeats recorded at the time of admission. The occurrence of abortion was recorded in 23 out of 149 cases, representing a rate of 15%.

In this study, 79.6% of the CRL in the groups under investigation had normal sac diameters. Except for one instance of normal diameter ending in miscarriage, every normal CRL continued past the first trimester. CRL's overall accuracy in predicting miscarriages was 99.1%, with a specificity of 100% and a sensitivity of 98.6%.

Varelas et al. ⁽⁴⁾ findings were corroborated, they observed that a high rate of fetal loss was associated with a short CRL (7–9, 12, and 15–16).

Only one instance with a normal diameter ended in miscarriage out of all the normal CRL cases in the current research that lasted past the first trimester. Our research has shown that CRL had a total accuracy of 99.1% in miscarriage prediction, with 98.6% sensitivity and 100% specificity.

Additionally, **Adija et al.** ⁽⁵⁾ demonstrated a correlation between CRL measurements taken between 5 and 10 weeks of gestation and the occurrence of fetal demise up to 14 weeks, in a study involving 316 spontaneous pregnancies. Nevertheless, it is challenging to compare their results with ours since they computed and reported the z-score as the divergence between the observed and predicted CRL.

Aziz et al. ⁽¹²⁾ performed a comparative analysis in which the CRL, measured between 6 and 9 weeks of gestation in 837 spontaneous abortion cases, was evaluated against reference values for the 10th to 90th percentiles in 227 in vitro fertilization (IVF) pregnancies. The findings revealed that when the CRL fell below the 50th percentile for the respective gestational age, there was a notably elevated risk of embryonic loss, with rates of 19.4% versus 3.3%.

Adija et al. ⁽⁵⁾ conducted a singular study focused on predicting early fetal demise in pregnancies with established gestational ages. By integrating first-trimester ultrasound parameters—including mean sac diameter, CRL, gestational age at the initial scan, and fetal heart rate—alongside maternal age, they attained an AUC of

0.87 for predicting fetal loss prior to 20 weeks of gestation. However, due to a small sample size, **Doubilet et al.** ⁽¹³⁾ were unable to confirm this association in a prospective study involving 99 pregnancies.

In this study, the EHR demonstrated an overall accuracy of 98.1%, with a specificity of 100% and a sensitivity of 97.5% for predicting first-trimester pregnancy outcomes. A statistically significant difference in EHR was observed between pregnancies that continued and those that ended in miscarriage, particularly in cases marked by bradycardia.

Fetal bradycardia, which is indicative of the imminent collapse of the circulatory system, is a warning indication of approaching fetal mortality. Another possible cause might be an underlying genetic defect linked to fetal bradycardia ⁽¹⁴⁾.

Suguna and Sukanya ⁽¹⁵⁾, stated that the rates of miscarriage were 100% if the embryonic heart rate was 70 BPM or less, 91% if it was between 70 and 79 BPM, and 79% if it was between 80 and 90 BPM. The study concluded that individuals who experienced sluggish heart rates (FHR <120 BPM) in the first trimester and were susceptible to miscarriage would also subsequently be at risk of losing their pregnancy.

Maged and Mostafa ⁽¹⁶⁾, conducted a study on 150 women who were unmarried and facing the possibility of miscarriage between weeks five and twelve of their pregnancy. They discovered that when the FHR dropped below the cutoff value of 110 BPM, the likelihood of miscarriage increased.

Mohamady et al. ⁽¹⁷⁾, examined a hundred cases of miscarriages between weeks seven and thirteen of gestation. The miscarried and the staying pregnant had substantially different FHRs ($P < 0.001$). Mean free heart rate (FHR) was 156.9 ± 20 BPM in the group that continued, and 122 ± 9 BPM in the group that miscarried.

CONCLUSION

Most embryos with CRLs of 2-5 millimeters can show cardiac activity. In over 80% of instances, non-visualization at this point is linked to embryonic death. Embryonic bradycardia and small CRL are linked to unfavorable pregnancy outcomes.

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Conflicts of interest: None.

REFERENCES

1. **Pils S, Stepien N, Kurz C et al. (2017):** Anti-Mullerian hormone is linked to the type of early pregnancy loss in idiopathic recurrent miscarriage: A retrospective cohort study. *Reprod Biol Endocrinol.*, 15, 60.
2. **Farag AM, Ibrahim A, Abdel Salam S (2018):** Ultrasonography and pregnancy outcome in threatened abortion: A prospective observational study. *Gynecol Obstet (Sunnyvale)*, 8: 481-5.
3. **Shetty A, Hegde D, Shetty B et al. (2015):** Yolk sac abnormalities –Is it a reliable indicator of abortions? – A prospective study in the population residing in rural setup of Mangaluru, Karnataka, India. *J Pharm Biomed Sci.*, 05(05): 380-384.
4. **Varelas E, Ahmad A, Halawa M (2018):** Yolk sac size and shape, gestational sac diameter, and embryonic heart rate as prognostic factors for first trimester outcome. *The Egyptian Journal of Hospital Medicine*, 73(9): 7418-7428.
5. **Adija P, Selvi C, Rai L et al. (2015):** Evaluation of yolk sac diameter and embryonic heart rate as prognostic factors of gestational outcome in early singleton pregnancies. *Scholars Journal of Applied Medical Sciences (SJAMS)*, 3(2A): 543-550.
6. **Abo Elwan H, Lebeda I, Elfawal F et al. (2019):** Prognostic factors of ultrasonography of yolk sac size and embryonic heart rate in first trimester pregnancy outcome. *Zagazig University Medical Journal, ZUMJ.*, 25(6): 801-808.
7. **Shahine L, Lathi R (2015):** Recurrent pregnancy loss: Evaluation and treatment. *Obstet. Gynecol. Clin N Am.*, 42; 117-134.
8. **Lebda I, El-Fawal F, El-samak A et al. (2019):** Prognostic factors of ultrasonography of yolk sac size and embryonic heart rate in first trimester pregnancy outcome. *ZUMJ.*, 25(6): 801-808.
9. **Hendriks E, MacNaughton H, MacKenzie M (2019):** First trimester bleeding: evaluation and management. *Am Fam Physician*, 99:166-174.
10. **Carp H, Guetta E, Dorf H (2016):** Embryonic karyotype in recurrent miscarriage with parental karyotypic aberrations. *Fertil Steril.*, 85:446-450.
11. **Falco G, Nagwani M, Tewari V et al. (2020):** The correlation of shape of yolk sac with spontaneous abortion- An ultrasonographic study. *EJMR.*, 5(2): 128-133
12. **Aziz S, Cho RC, Baker DB et al. (2008):** Five-millimeter and smaller embryos without embryonic cardiac activity outcomes in women with vaginal bleeding. *J Ultrasound Med.*, 27: 1559-1561.
13. **Doubilet P, Benson C (2015):** Outcome of first-trimester pregnancies with slow embryonic heart rate at 6-7 weeks gestation and normal heart rate by 8 weeks in the US. *Radiology*, 236(2):643.
14. **Liao A, Snijders R and Geerts L (2020):** Fetal heart rate in chromosomally abnormal fetuses. *Ultrasound Obstet Gynecol.*, 16:610.
15. **Suguna B, Sukanya K (2019):** Yolk sac size & shape as predictors of first-trimester pregnancy outcome: A prospective observational study. *Journal Gynecol Obstet Hum Reprod.*, 48:159-164.
16. **Maged A, Mostafa W (2013):** Biochemical and ultrasonographic predictors of outcome in threatened abortion. *Middle East Fertility Society Journal*, 18 (3): 177-181.
17. **Mohamady M, Fattah GA, Elkatian E et al. (2016):** Correlation of serum CA-125 & progesterone levels with ultrasound markers in the prediction of pregnancy outcome in threatened miscarriage. *International Journal of Fertility & Sterility*, 9(4): 506.