Role of Serum β-hCG and First Trimester Ultrasonographic Parameters in Predicting Mid-trimester Pregnancy Outcomes: A Prospective Cohort Study

SHANMUGA PRIYA RAJAMNICKAM[1], SAJEETHAKUMARI RAVEENDRAN[2], SASWATI TRIPATHY[3], ANURADHA MURUGESAN[4], DEBORAL PANNEERSELVAM[5]

ABSTRACT

Introduction: One of the concerns in pregnant women is the risk of miscarriage and the psychological sequelae that follow. Screening in early pregnancy can identify future miscarriages in asymptomatic pregnancies.

Aim: To study the role of serum Beta-Human Chorionic Gonadotropin (β-hCG) doubling and ultrasonic parameters like Yolk Sac Diameter (YSD), Gestational Sac Diameter (GSD), and Crown-Rump Length (CRL) in predicting mid-trimester pregnancy outcomes.

Materials and Methods: A prospective cohort study was conducted at SRM Medical College and Hospital in Tamil Nadu, India, among 381 antenatal women between 6-10 weeks of gestation for a period of two years from December 2017 to July 2019. At baseline, parameters like serum β-hCG doubling titer at 48 hours and ultrasound parameters like YSD, GSD, and CRL were evaluated. The participants were followed-up until 20 weeks of gestation. The results were statistically analysed using sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

Results: The mean age of the women included in the study was 25.89±4.2 years, with the majority of women belonging to the 21-29 years age group. Among the enrolled pregnant women, 347 had normal outcomes while 34 experienced pregnancy failure. The results indicated that β-hCG was the strongest predictor of pregnancy outcomes with a sensitivity of 52.9%, specificity of 100%, PPV of 100%, and NPV of 95.6%. YSD predicted loss rates with a sensitivity of 50%, specificity of 97.1%, PPV of 62.9%, and NPV of 95.2%. GSD predicted miscarriage with a sensitivity of 17.6%, specificity of 97.4%, PPV of 40%, and NPV of 92.3%. CRL predicted miscarriage with a sensitivity of 30.5%, specificity of 97.9%, PPV of 61.1%, and NPV of 93.2%.

Conclusion: β-hCG, YSD, GSD, and CRL were found to be statistically significant in predicting abnormal pregnancy outcomes. Among the four, β-hCG proved to be the best predictor.

Keywords: β-human chorionic gonadotropin, Crown-rump length, Gestational sac diameter, Yolk sac diameter

INTRODUCTION

A successful pregnancy is one of the milestones in any woman's life. Here, one of the concerns is the risk of miscarriage, which is devastating to women, especially in developing countries where lack of awareness and poor diagnostic approaches add to the problem. People must try to widen the scope of predicting and diagnosing it early, thereby terminating a pregnancy that doesn't stand a chance of success [1,2]. Early warning of probable miscarriage can modify the psychological morbidity associated with it. The literature outlines various biochemical markers for outcome prediction, namely Alpha Fetoprotein (AFP), β-hCG, progesterone, CA-125, Pregnancy-associated Plasma Protein A (PAPPA), Estradiol (E2), activin A, inhibin A, Placental Growth Factor (PIGF), soluble Fms-like tyrosine kinase 1 (sFlt-1), etc., [1]. Subjecting women to undergo all these tests can be cumbersome and misleading. In the era of modern medicine, ultrasound, especially Transvaginal Ultrasonography (TVS), has revolutionised the field of obstetrics. However, ultrasound imaging is operator-dependent, and the quality of the diagnosis depends on skill and experience. CRL, YSD, GSD are three important measurements normally studied in early USG for gestational age calculation [3]. Hence, the present study was aimed to study the role of serum β-hCG doubling and ultrasonic parameters like YSD, GSD, and CRL in predicting mid-trimester pregnancy outcomes.

MATERIALS AND METHODS

A prospective cohort study was conducted at SRM Medical College and Hospital, Tamil Nadu, India, among 381 antenatal women between 6-10 weeks of gestation for a period of two years from December 2017 to July 2019. Ethical clearance was obtained by the Institutional Ethical Committee (IEC) to conduct the study (No: 1405/IEC/2018), and informed consent was obtained from the participants. Consecutive samples that met the study criteria were included.

Inclusion criteria: A total of 414 pregnant women between 18-35 years of age with a single intrauterine gestation of 6-10 weeks attending the antenatal Outpatient Department (OPD) were included in the study. Out of these, 33 were lost during follow-up, and the remaining 381 were included in the study.

Exclusion criteria: Women with ectopic pregnancy, multiple pregnancies, molar pregnancy, structural anomalies of the uterus and cervix, and those with known endocrine and immunological disorders causing abnormal pregnancy outcomes were excluded from the study.
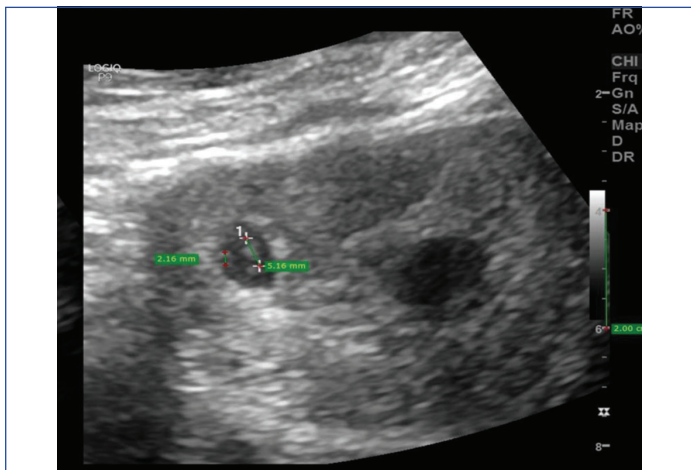
Study Procedure

A 7.7 MHz transducer was used to perform TVS. Parameters such as YSD, GSD, CRL, and Foetal Heart Rate (FHR) were measured. The CRL was measured as the greatest length in a straight line from the cranial to the caudal end of the body in the straightest possible position of the embryo. GSD was determined by measuring the length, width, and height of the sac and then dividing by 3. The YSD was measured from the inner to the inner diameter of the sac without including the walls of the sac in the measurement [Table/Fig-1]. YSD <2 mm and >6 mm, GSD, and CRL values >2SD/<2SD of the mean

were considered abnormal [2]. Serum β-hCG was done at the first visit between 6-10 weeks and repeated after 48 hours to check for doubling, i.e., atleast 66% of the initial β-hCG. Patients who underwent TVS and had two β-hCG values were asked to review at 12 weeks, 16 weeks, and 20 weeks for follow-up. Patients were informed to report immediately if they experienced symptoms such as abdominal pain or vaginal bleeding. Women with symptoms of threatened abortion were advised bed rest, started on progesterone therapy, and followed-up weekly until their condition improved. NT scan (nuchal translucency scan) and anomaly scan were performed at 12 and 20 weeks, respectively. Any pregnancy diagnosed with an anomalous foetus in these USG scans was terminated. A normal outcome was defined as a pregnancy that continued beyond 20 weeks. An abnormal outcome was defined as a pregnancy that ended in unintentional miscarriage, irrespective of aetiology.

[Table/Fig-1]: Ultrasonography (USG) of CRL, GSD and YSD.
CRL: Crown-rump length; GSD: Gestational sac diameter; YSD: Yolk sac diameter

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 19.0. Sensitivity, specificity, PPV, NPV, and Fisher's-exact probability were used to determine the relationship between β-hCG, YSD, GSD, CRL, and abnormal pregnancy outcomes.

RESULTS

The mean age of the women included in the study was 25.89±4.2 years, with the majority of women belonging to the 21-29 years age group [Table/Fig-2]. Out of the total 381 pregnancies in the present study, 34 women (9%) subsequently miscarried. Among the 34 miscarried pregnancies, 25 women (98%) had early pregnancy loss before 12 weeks of gestation, and 9 (2%) had mid-trimester pregnancy losses (between 12 weeks-20 weeks). Among the early pregnancy losses, 20 (59%) had spontaneous abortions, while

[Table/Fig-2]: Distribution of pregnancy outcomes by maternal age.

14 (38%) were missed abortions. One pregnancy was terminated due to Non Immune Foetal Hydrops (NIFH).

The peak incidence of miscarriage was observed in women over 30 years of age in 8 (12%) women, followed by women under 20 years old 4 (11%). When considering the number of prior pregnancy losses, the miscarriage rates steadily increased from 2 (3.2%) in pregnancies with one prior loss to 3 (100%) in pregnancies with four prior losses. There was only one female with five prior pregnancy losses who successfully completed her pregnancy. In the present study, majority of miscarriages occurred between 7-8+6 weeks 20 (24%). Only 16 (5%) out of 347 pregnancies with a normal rise in β-hCG subsequently miscarried [Table/Fig-3]. These results indicate that β-hCG was the strongest predictor of pregnancy outcomes, with a sensitivity of 52.9%, specificity of 100%, PPV of 100%, and NPV of 95.6% [Table/Fig-4].

β-hCG doubling	Pregnancy outcomes		Total (N)
	Normal	Miscarriage	
	(n) %	(n) %	
Present	347 (95)	16 (5)	363
Absent	-	18 (100)	18
Total	347	34	381

[Table/Fig-3]: Comparison of pregnancy outcomes by β-hCG doubling.
β-hCG: Beta human chorionic gonadotropin, n: Number of antenatal women

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Fisher's exact probability	p-value
β-hCG doubling (-)	52.9	100	100	95.6	192.82	0.001
Abnormal GSD	17.6	97.4	40	92.3	18.55	0.0001
Abnormal YSD	50	97.1	62.9	95.2	104.41	0.0001
Abnormal CRL	30.5	97.9	61.1	93.2	63.31	0.0001

[Table/Fig-4]: Statistical analysis of pregnancy outcomes using all four parameters.
β-hCG: Beta human chorionic gonadotropin; GSD: Gestational sac diameter; YSD: Yolk sac diameter; CRL: Crown-rump length; PPV: Positive predictive value; NPV: Negative predictive value

In the present study, authors observed higher pregnancy loss rates of 30% and 83% in patients with YSD <2 mm and >6 mm, respectively. This rate was relatively low (5%) in cases of patients with normal YSD (between 2-6 mm) [Table/Fig-5]. Similar trends were noted for GSD and CRL, although the differences were not significant [Table/Fig-6,7].

YSD (in mm)	Pregnancy outcome		Total
	Normal outcome	Miscarriage	
	n (%)	n (%)	
<2	7 (70)	3 (30)	10
2-6	337 (95)	17 (5)	354
>6	3 (17)	14 (83)	17
Total	347 (91)	34 (9)	381

[Table/Fig-5]: Comparison of pregnancy outcomes by YSD.
YSD: Yolk sac diameter; n: Number of antenatal women
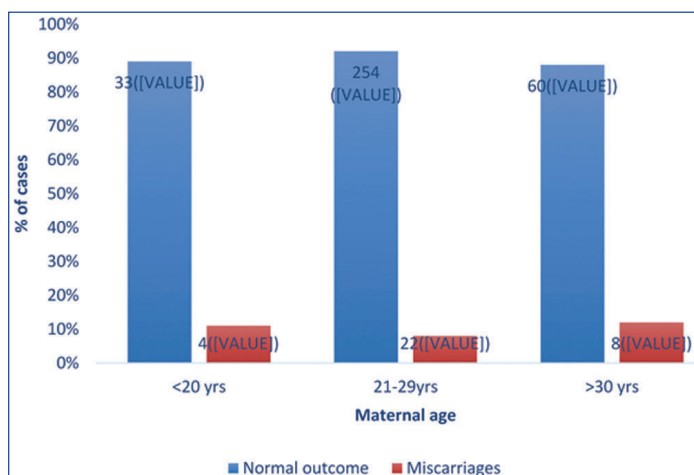
GSD	Normal outcome n (%)	Abnormal outcome n (%)	Total n (%)
<2 SD	2 (0.57)	0	2 (0.52)
Normal	345 (99.42)	34 (100)	379 (99.47)
>2 SD	0	0	0

[Table/Fig-6]: Statistical analysis of GSD (N=381).
GSD: Gestational sac diameter; n: Number of antenatal women; SD: Standard deviation

CRL	Normal outcome n (%)	Abnormal outcome n (%)	Total
<2SD	11 (3.17)	0	11
Normal	332 (95.67)	34 (100)	366
>2SD	4 (1.15)	0	4

[Table/Fig-7]: Statistical analysis of CRL.
CRL: Crown rump length; n: Number of antenatal women; SD: Standard deviation

Analysing these four parameters, all of them predicted miscarriage with statistical significance. Among them, β-hCG proved to be the strongest parameter with the highest sensitivity (52.9%), specificity (100%), and PPV (100%). Among the ultrasonographic parameters, YSD was a better predictor, as it had the highest sensitivity of 50% and PPV of 62.9% [Table/Fig-4].

DISCUSSION

The prevalence of miscarriage in the Indian population is about 10%-15% [1]. Out of a total of 381 pregnancies, 34 women (9%) subsequently miscarried. In the present study, the miscarriage rates were 4 (11%) in women under 20 years old, 22 (8%) in the age group between 21 to 29 years, and peaked at 8 (12%) in women over 30 years of age. These findings are consistent with studies by Siddiqi TA et al., who noted a significantly greater incidence of pregnancy loss after 34 years of age compared to women under 34 years old (11.1% versus 4.4%) [2], and by Kajii T et al., [3]. However, Makrydimas G et al., reported higher pregnancy loss rates after 35 years - 4% in women under 20 years old and 20% in women over 35 years old [4]. The incidence of euploid abortion increased significantly when maternal age exceeded 35 years, as reported by Stein in New York Academic Press [5]. However, in the present study, cause of miscarriage was not studied at the chromosomal level.

Present research revealed that in women with prior miscarriages, the pregnancy loss rate increased with the number of previous losses - reaching 100% in women with a history of four prior losses. However, the authors also observed a woman with five previous pregnancy losses in the present study who had a successful outcome. This finding is in accordance with studies by Magnus MC et al., [6], which showed that the risk of miscarriage was increased in women whose previous pregnancy ended in miscarriage {Odds Ratio (OR) 1.65, 95% Confidence Interval (CI) 1.59 to 1.71} compared to women with no previous pregnancy loss.

After an ultrasound detects FHR, the risk of pregnancy loss is significantly lower. In the present study, miscarriage rates peaked at the 8th week of gestation (14%) and subsequently decreased in the following weeks (8% at the 9th and 10th week). Similarly, the results of Makrydimas G et al., showed loss rates of 10% at six weeks of gestation, declining to 3% at 10 weeks of gestation [4]. This proposition is also supported by the study of Ammon Avalos L et al., which stated that miscarriage rates decline with advancing gestational age [7]. GSD showed a positive association with the prediction of miscarriage, which was statistically significant. Studies by Nyberg DA et al., Makrydimas G et al., and Falco P et al., demonstrated loss rates of 73%, 73.7%, and 93%, respectively, with abnormal GSD (p=0.0001) [8-10]. Therefore, GSD may have a role as a screening tool in predicting miscarriages. In a study by Shahin AHE et al., the mean GSD in those with early pregnancy loss was 2.02±1.26 mm, while mothers who successfully completed the first trimester had a GSD of 4.15±1.84 mm [11]. However, due to the higher frequency of first-trimester losses in their study, present study was unable to demonstrate such a significant correlation.

The authors concluded that YSD predicts loss rates with a sensitivity of 50%, specificity of 97.1%, PPV of 62.9%, and NPV of 95.2%. This is similar to studies conducted by Lindsay DJ et al., Stampone C et al., Küçük T et al., Chama C et al., Suguna B and Sukanya K, where the sensitivity of YSD in predicting pregnancy loss rates was 15.6%, 68.7%, 65%, 91.4%, and 62.3%, respectively. The specificity in these studies was 97.4%, 99%, 97%, 66%, and 64.1%, respectively [12-16]. Although authors agree that abnormal YS shape predicts abnormal pregnancy outcomes, the definitions for abnormal YS were not definitely mentioned and hence were not included in the present study [10,17,18]. In contrast to the above studies, Makrydimas G et al., and Maged AM and Al Mostafa W

could not find a significant relation between abnormal YSD and miscarriage rates (p=0.06) [4,19]. Detti L et al., also affirmed that a larger yolk sac could predict spontaneous abortions atleast one week prior in 43% of women. The period of loss was advanced in pregnancies with a smaller YSD compared to a larger one, confirming that an enlarged yolk sac is a better predictor of adverse pregnancy outcome [20].

In a study conducted by Barnhart KT et al., atleast 53% increase in β-hCG doubling in two days was observed, which is consistent with the present study where the authors observed 16 (47.05%) cases of β-hCG doubling out of 34 pregnant women [21]. This finding is also supported by Porat S et al., who found that 76.47% of miscarriage subjects had β-hCG <150 mIU/mL. Single measurements of β-hCG rather than serial measurements affected their results [22]. Thus, β-hCG can be considered the strongest predictor of miscarriage with 100% specificity and 100% PPV.

Limitation(s)

It was a single-centre study, and demographic features like socioeconomic status of the participants were not included. The duration of gestational age studied was in a wide range, i.e., 6-10 weeks of gestation, rather than a specific GA. In terms of YS biometry, the authors only analysed the size and did not consider its shape.

CONCLUSION(S)

The β-hCG doubling, YSD >6 mm, GSD <2SD or >2SD, and CRL <2SD were found to be statistically significant in predicting abnormal pregnancy outcomes. Among these parameters, β-hCG doubling was found to be a better predictor and should be routinely employed in clinical practices for risk prediction. Additionally, YSD proved to be superior in predicting miscarriage among the sonographic parameters. Reliable prediction of miscarriage in the first trimester could potentially improve pregnancy outcomes by allowing closer prenatal monitoring, earlier diagnosis, and expeditious interventions. Therefore, these parameters can be used in counselling patients regarding the prognosis of their pregnancy. Progesterone support can be considered in cases of absent doubling and abnormal sonographic parameters.

Acknowledgement

REFERENCES

[1] Patki A, Chauhan N. An epidemiology study to determine the prevalence and risk factors associated with recurrent spontaneous miscarriage in India. The Journal of Obstetrics and Gynecology of India. 2016;66(5):310-15.

[2] Siddiqi TA, Caligaris JT, Miodovnik M, Holroyde JC, Mimouni F. Rate of spontaneous abortion after first trimester sonographic demonstration of fetal cardiac activity. Am J Perinatol. 1988;5(1):01-04.

[3] Kajii T, Ferrier A, Niikawa N, Takahara H, Ohama K, Avirachan S. Anatomic and chromosomal anomalies in 639 spontaneous abortuses. Hum Genet. 1980;55(1):87-98.

[4] Makrydimas G, Sebire NJ, Lolis D, Vlassis N, Nicolaides KH. Fetal loss following ultrasound diagnosis of a live fetus at 6-10 weeks of gestation. Ultrasound Obstet Gynecol. 2003;22(4):368-72.

[5] Stein Z, Susser E, Kline J. Maternal age and spontaneous abortion. Human Embryonic and Fetal Death. 1980;103.

[6] Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: Prospective register based study. BMJ. 2019;364:l869.

[7] Ammon Avalos L, Galindo C, Li DK. A systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Res A Clin Mol Teratol. 2012;94(6):417-23.

[8] Nyberg DA, Mack LA, Laing FC, Patten RM. Distinguishing normal from abnormal gestational sac growth in early pregnancy. J Ultrasound Med. 1987;6(1):23-27.

[9] Falco P, Milano V, Pilu G, David C, Grisolia G, Rizzo N, et al. Sonography of pregnancies with first-trimester bleeding and a viable embryo: A study of prognostic indicators by logistic regression analysis. Ultrasound in Obstetrics and Gynecology. 1996;7(3):165-69.

[10]	Tan S. Abnormal sonographic appearances of the yolk sac: Which can be associated with adverse perinatal outcome? Med Ultrason. 2014;16(1):15-20.

[11]	Shahin AHE, Elmasry MES, Gad M. Yolk sac size and shape, gestational sac diameter, and embryonic heart rate as prognostic factors of first-trimester pregnancy outcomes. Menoufia Medical Journal. 2022;35(2):776.

[12]	Lindsay DJ, Lovett IS, Lyons EA, Levi CS, Zheng XH, Holt SC, et al. Yolk sac diameter and shape at endovaginal US: Predictors of pregnancy outcome in the first trimester. Radiology. 1992;183(1):115-18.

[13]	Stampone C, Nicotra M, Muttinelli C, Cosmi EV. Transvaginal sonography of the yolk sac in normal and abnormal pregnancy. Journal of Clinical Ultrasound. 1996;24(1):03-09.

[14]	Küçük T, Duru NK, Yenen MC, Dede M, Ergün A, Başer İ. Yolk sac size and shape as predictors of poor pregnancy outcome. J Perinat Med. 1999;27(4):316-20.

[15]	Chama C, Marupa J, Obed J. The value of the secondary yolk sac in predicting pregnancy outcome. J Obstet Gynaecol (Lahore). 2005;25(3):245-47.

[16]	Suguna B, Sukanya K. Yolk sac size & shape as predictors of first trimester pregnancy outcome: A prospective observational study. J Gynecol Obstet Hum Reprod. 2019;48(3):159-64.

[17]	Cho FN, Chen SN, Tai MH, Yang TL. The quality and size of yolk sac in early pregnancy loss. Aust N Z J Obstet Gynaecol. 2006;46(5):413-18.

[18]	Richardson A, Gallos I, Dobson S, Campbell BK, Coomarasamy A, Raine-Fenning N. Accuracy of first-trimester ultrasound in diagnosis of intrauterine pregnancy prior to visualization of the yolk sac: A systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;46(2):142-49.

[19]	Maged AM, Al Mostafa W. Biochemical and ultrasonographic predictors of outcome in threatened abortion. Middle East Fertil Soc J. 2013;18(3):177-81.

[20]	Detti L, Francillon L, Christiansen ME, Peregrin-Alvarez I, Goedecke PJ, Bursac Z, et al. Early pregnancy ultrasound measurements and prediction of first trimester pregnancy loss: A logistic model. Sci Rep. 2020;10(1):1545.

[21]	Barnhart KT, Sammel MD, Rinaudo PF, Zhou L, Hummel AC, Guo W. Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. Obstetrics and Gynecology. 2004;104(1):50-55.

[22]	Porat S, Savchev S, Bdolah Y, Hurwitz A, Haimov-Kochman R. Early serum β-human chorionic gonadotropin in pregnancies after in vitro fertilization: Contribution of treatment variables and prediction of long-term pregnancy outcome. Fertil Steril. 2007;88(1):82-89.

PARTICULARS OF CONTRIBUTORS:
1.	Junior Resident, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India.
2.	Professor, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India.
3.	Professor, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India.
4.	Professor and Head, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India.
5.	Research Scholar, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sajeethakumari Raveendran,
Professor, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu-603203, Tamil Nadu, India.
E-mail: sajeethaprabhakar@gmail.com

AUTHOR DECLARATION:
• Financial or Other Competing Interests: None
• Was Ethics Committee Approval obtained for this study?   Yes
• Was informed consent obtained from the subjects involved in the study?   Yes
• For any images presented appropriate consent has been obtained from the subjects.   NA