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Original Article

Obstetrics and Gynaecology Section

Identification of Effective Model for Prediction of Ovarian Malignancy Risk using Models like Risk of Malignancy Index, Logistic Regression, International Ovarian Tumour Analysis- Simple Rules

SR RAMYA

ABSTRACT

Introduction: Ovarian tumour is not a single entity it is a spectrum of neoplasm involving variety of histological tissues. Use of mathematical formula as malignancy index which is based on logistic model, menopausal status, serum levels of Cancer Antigen 125 (CA-125) and ultrasound findings in a score system is not so popular which can be a useful predictor for diagnosing and monitoring the progression of ovarian malignancy.

Aim: To determine the effectiveness of the three models i.e., Risk of Malignancy Index (RMI-1,2,3 and 4), Logistic Regression 2 (LR-2), International Ovarian Tumour Analysis (IOTA) - simple rules in predicting ovarian malignancy.

Materials and Methods: This prospective cohort observational study was conducted in Department of Obstetrics and Gynaecology at Saveetha Medical College and Hospital, Tamil Nadu, India, from June 2017 to July 2018. The study included a total of 70 female subjects with ovarian mass. Information obtained by investigations, ultrasound was used to predict the risk of malignancy by using the three models {Risk of Malignancy Index (RMI-1, 2, 3 and 4), Logistic Regression 2 (LR-2), International Ovarian Tumour Analysis (IOTA)-simple rules}. CA-125 level was considered as primary outcome variable. Study group histopathology impression (malignant vs benign) was considered as primary explanatory variable. The result from the above models was compared with the postoperative histopathological report. The sensitivity and specificity of each model was also identified.

Results: Majority of the study participants 49 (70%) were in premenopausal status and only 21 (30%) were in menopausal status. The mean CA-125 level was 108.82±233.13 in the study population (95% CI: 53.23-164.41). Among the 70 study subjects, 53 (75.70%) patients were RMI-1 benign and only 17 (24.30%) were RMI-1 malignant. Majority of the study participants 44 (60%) were IOTA impression benign and only 23 (40%) were IOTA malignant. The difference in the proportion of IOTA-simple rules between histopathology impression was statistically significant (p-value <0.001). The sensitivity of IOTA-simple rules in predicting malignant histopathology was 92%, specificity was 90.48%, diagnostic accuracy was 91.04%.

Conclusion: For early risk stratification of adnexal masses, IOTA-simple rules can be used as a screening tool due to its high sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

Keywords: CA-125, Hysterectomy, Index, Malignant tumours, Menopausal status

INTRODUCTION

Ovaries start to develop by the 5th week of intrauterine life. The ovarian differentiation is determined by the presence of a determinant located on the gene of the short arm of X-sex chromosome though the autosomes are also involved in the ovarian development. Two intact sex chromosomes XX are necessary for the development of the ovary [1]. Ovarian tumour is not a single entity it is a range of neoplasm including diversity of histological tissues ranging from epithelial tissues, connective tissues, specialized hormone secreting cells to germinal and embryonal cells [1]. The most common are epithelial tumours forming 80% of all tumours are benign [1]. Of all malignant tumours 90% are epithelial in origin, 80% primary in the ovary and 20% secondary from the breasts, gastrointestinal tracts and colon. Benign tumours can become secondary malignant. The average age of borderline tumours is approximately 46 years [2,3]. Epithelial ovarian cancer is associated with low parity and fertility. Because parity is inversely related to the risk of ovarian cancer, having at least one child is protective for the disease, with risk reduction of 0.3-0.4% [3,4].

Unopposed oestrogen and obesity are also likely to be risk factor for ovarian tumours [5]. The early age of menarche and late menopause are associated with an increase in ovarian cancer risk, because both increase the number of ovulatory cycles [6]. Ovulation induction for more than 6 cycles doubles the risk of ovarian carcinoma [7]. Most hereditary ovarian cancers result from germ line mutations in the *BRCA1* and *BRCA2* genes. The development of a mathematical formula using a logistic model, incorporating menopausal status, serum levels of a glycoprotein called CA-125 and ultrasound findings in a score system, has been described in the literature in the form of malignancy index [5-7]. The present study was conducted with an aim to determine the effectiveness of the following three models in the preoperative prediction of risk of ovarian malignancy by comparing the results with the postoperative histopathological report- Risk of Malignancy Index (RMI-1,2,3 and 4), Logistic Regression 2 (LR-2), International Ovarian Tumour Analysis (IOTA)- simple rules. Also, to analyse which model relates best with postoperative histopathological report.

MATERIALS AND METHODS

This prospective cohort observational study was conducted in Department of Obstetrics and Gynaecology at Saveetha Medical College and Hospital, Tamil Nadu, India, from June 2017 to July 2018. The ethical clearance by Institutional Ethics Committee and informed consent by patients included in the study were obtained. Convenient

sampling was used for sample selection. Patient with history suggestive of ovarian tumour or ultrasound finding of an ovarian mass and subsequently underwent surgery for the same were included in the study. A total of 70 patients were selected for the study.

Inclusion criteria: Patients presented with ultrasound finding of an ovarian mass (size >5 cm, with internal septations, with solid components, ascites) were included in the study.

Exclusion criteria: Patients presented with physiological cyst (unilateral, simple cyst of <5 cm, with clear fluid), pregnant women, patients who refuse transvaginal ultrasound, those who did not undergo surgical removal of mass at Saveetha Medical College and Hospital, Tamil Nadu, were excluded from the study.

Procedure

A brief history which included the patient's demographic details was obtained details of general examination, gynaecological examination, per rectal examination were done. Blood investigation for serum CA-125 level was done. About 2 mL of blood was collected from all the subjects, in a red topped plain tube which was used for this biochemical test. First a transabdominal ultrasound was done followed by a transvaginal ultrasound. The findings were entered in the proforma. All the above information was used to predict the malignancy of the ovarian tumour using the three models (RMI-1, 2, 3 and 4, LR-2 and IOTA- simple rule). The result (benign/malignant) from the above models was compared with the postoperative histopathological report, and thereby the most effective model in predicting the malignancy of an ovarian tumour was identified. The histopathological report was taken as standard against which the results from various models were compared. The sensitivity and specificity of each model was also identified.

Risk using models like risk of malignancy index: RMI Index is based on mathematical formula using logistic model, incorporating menopausal status, serum levels of a glycoprotein called CA-125 and ultrasound findings in a score system, in the form of malignancy index. 'Postmenopause' is defined as amenorrhoea for more than one year or a woman over 50 years of age who underwent hysterectomy. CA-125 was measured in IU/mL. Ultrasound findings like, bilaterality, multilocularity, solid areas, ascites, intra-abdominal metastasis-one point was given for each feature and the RMI was calculated using the formula RMI=U×M×CA125 U- ultrasound score M- menopausal status CA125 [3-5].

Logistic regression-2: Model 2 is based on age of the patient (In years), the presence of ascites, the presence of blood flow within a papillary projection, the largest diameter of a solid component (in mm), the irregular internal cyst walls, the presence of acoustic shadow. A value above 0.10 was considered as malignant by LR2 [3-5].

International ovarian tumour analysis- Simple rules

Ultrasound features for benign and malignant tumours [4-6]:

Benign tumour

- B1-Unilocular cyst
- B2-Presence of solid components, maximum diameter

Malignant tumour

Categorised as follows based on the histopathological features and score

- M1-Irregular solid tumour;
- M2-Presence of ascites;
- M3-Atleast four papillary structures;
- M4-Irregular multilocular solid tumour, maximum diameter >100 mm;
- M5-Very strong blood flow (colour score 4).

Rule

- Rule 1-one or more Malignant features were present in the absence of a benign feature, classified the mass as malignant.
- Rule 2-if one or more benign features were present in the absence of a malignant feature, classified the mass as benign.
- Rule 3- if both malignant and benign features were present, or none of the features was present, the simple rules were inconclusive.

STATISTICAL ANALYSIS

The CA-125 level was considered as primary outcome variable. Study group histopathology impression (malignant vs benign) was considered as primary explanatory variable. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. All quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk's test was also conducted to assess normal distribution. Shapiro-wilk's test p-value of >0.05 was considered as normal distribution. The utility of CA-125 level in predicting malignancy was assessed by Receiver Operative Curve (ROC) analysis. Area under the ROC curve along with it's 95% Confidence Interval (CI) and p-value was presented. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening tests of RMI-1, RMI-2, RMI-3, RMI-4, LR2 and IOTA-simple rules along with their 95% CI were presented. The p-value <0.05 was considered statistically significant. IBM Statistical Package for the Social Sciences (SPSS) version 22.0 was used for statistical analysis.

RESULTS

A total 70 people were included in the analysis. Majority of the study participants 49 (70%) were in premenopausal status and only 21 (30%) were in menopausal status. The mean CA-125 level was 108.82±233.13 in the study population, minimum level was 5 and maximum level was 1000 (95% CI: 53.23- 164.41). Majority of the study participants 42 (62.70%) were histopathology impression benign and only 25 (35.70%) were histopathology impression malignant. Among all the participants of the study three patients had a borderline tumour in histopathological examination. Therefore, for all comparisons only 67 patients were considered and sensitivity and specificity was calculated accordingly.

Majority of the study participants 52 (71.40%) were RMI-2 benign and only 15 (28.60%) were RMI-2 malignant. Majority of the study participants 54 (75.70%) were RMI-3 benign and only 13 (24.30%) were RMI-3 malignant. Majority of the study participants 52 (71.4%) were RMI-Impression benign and only 15 (28.6%) were RMI-4 malignant. Majority of the study participants 52 (64.30%) were LR-2 impression benign and only 15 (35.70%) were LR-2 malignant. Majority of the study participants 44 (60%) were IOTA impression benign and only 23 (40%) were IOTA malignant.

Among the malignant histopathology, 13 (52%) participants had malignant RMI-1 and remaining 12 (48%) participants had benign. Among the benign histopathology impression, 4 (9.52%) participants had malignant RMI-1 and remaining 38 (90.48%) participants had benign. The difference in the proportion of RMI-1 between histopathology impression was statistically significant (p-value=0.001) [Table/Fig-1].

RMI-1	Histopathology impression		Chi-square	p-value
	Malignant (N=25)	Benign (N=42)		
Malignant	13 (52%)	4 (9.52%)	14.933	<0.001
Benign	12 (48%)	38 (90.48%)		

[Table/Fig-1]: Comparison of histopathology impression with RMI-1.
*Total 70 patients were considered for the study. As three patients had borderline malignant in histopathology examination we did not consider them calculation of RMI, LR and IOTA and further comparisons

The sensitivity of RMI-1 in predicting malignant histopathology was 52% (95% CI 31.31% to 72.20%), specificity was 90.48% (95% CI 77.38% to 97.34%) [Table/Fig-2].

Parameters	Value	95% CI	
		Lower	Upper
Sensitivity	52.00%	31.31%	72.20%
Specificity	90.48%	77.38%	97.34%
False positive rate	9.52%	2.66%	22.62%
False negative rate	48.00%	27.80%	68.69%
Positive predictive value	76.47%	50.10%	93.19%
Negative predictive value	76.00%	61.83%	86.94%
Diagnostic accuracy	76.12%	64.14%	85.69%

[Table/Fig-2]: Predictive validity of RMI-1 in predicting histopathology impression.

Among the malignant histopathology, 15 (60%) participants had malignant RMI-2 and remaining 10 (40%) participants had benign. Among the benign histopathology, 5 (11.9%) participants had malignant RMI-2 and remaining 37 (88.1%) participants had benign. The difference in the proportion of RMI-2 between histopathology impression was statistically significant (p-value <0.001) [Table/Fig-3].

The sensitivity of RMI-2 in predicting malignant histopathology was 60% (95% CI 40.80% to 79.2%), specificity was 88.1% (95% CI 78.31% to 97.9%) [Table/Fig-4].

RMI-2 and 4	Histopathology impression		Chi-square	p-value
	Malignant (N=25)	Benign (N=42)		
Malignant	15 (60%)	5 (11.9%)	17.312	<0.001
Benign	10 (40%)	37 (88.1%)		

[Table/Fig-3]: Comparison of histopathology impression with RMI-2 and RMI-4.
*Total 70 patients were considered for the study. As three patients had borderline malignant in histopathology examination we did not consider them calculation of RMI, LR and IOTA and further comparisons

Parameters	Value	95% CI	
		Lower	Upper
Sensitivity	60.00%	40.80%	79.2%
Specificity	88.1%	78.31%	97.9%
False positive rate	11.9%	2.11%	21.7%
False negative rate	40.00%	20.80%	59.2%
Positive predictive value	75.00%	56.02%	94.0%
Negative predictive value	78.7%	66.99%	90.4%
Diagnostic accuracy	77.6%	67.63%	87.6%

[Table/Fig-4]: Predictive validity of histopathology impression as compared to RMI-2 and RMI-4.

Among the malignant histopathology impression, 13 (52%) participants had malignant RMI-3 and remaining 12 (48%) participants had benign. Among the benign histopathology impression, 4 (9.5%) participants had malignant RMI-3 and remaining 38 (90.5%) participants had benign. The difference in the proportion of RMI-3 between histopathology impression was statistically significant (p-value <0.001) [Table/Fig-5].

RMI-3	Histopathology impression		Chi-square	p-value
	Malignant (N=25)	Benign (N=42)		
Malignant	13 (52%)	4 (9.5%)	14.933	<0.001
Benign	12 (48%)	38 (90.5%)		

[Table/Fig-5]: Comparison of histopathology impression with RMI-3.
*Total 70 patients were considered for the study. As three patients had borderline malignant in histopathology examination we did not consider them calculation of RMI, LR and IOTA and further comparisons

The sensitivity of RMI-3 in predicting malignant histopathology was 52% (95% CI 32.42% to 71.6%), specificity was 90.5% (95% CI 81.63% to 99.4%) [Table/Fig-6].

Among the malignant histopathology impression, 15 (60%) participants had malignant RMI-4 and remaining 10 (40%) participants had benign.

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	52.00%	32.42%	71.6%
Specificity	90.5%	81.63%	99.4%
False positive rate	9.5%	0.63%	18.4%
False negative rate	48.0%	28.42%	67.6%
Positive predictive value	76.5%	56.34%	96.7%
Negative predictive value	76.0%	64.16%	87.8%
Diagnostic accuracy	76.1%	65.91%	86.3%

[Table/Fig-6]: Predictive validity of histopathology impression as compared to RMI-3.

Among the benign histopathology impression, 5 (11.9%) participants had malignant RMI-4 and remaining 37 (88.1%) participants had benign. The difference in the proportion of RMI-4 impression between histopathology impression was statistically significant (p-value <0.001) [Table/Fig-3].

The sensitivity of RMI-4 impression in predicting malignant histopathology was 60% (95% CI 40.80% to 79.2%), specificity was 88.1% (95% CI 78.31% to 97.9%) [Table/Fig-4].

Among the malignant histopathology impression, 15 (60%) participants had malignant LR-2 and remaining 10 (40%) participants had benign. Among the benign histopathology impression, 5 (11.9%) participants had malignant LR-2 and 37 (88.1%) participants had benign. The difference in the proportion of LR-2 between histopathology impression was statistically significant (p-value <0.001) [Table/Fig-7].

LR-2	Histopathology impression		Chi-square	p-value
	Malignant (N=25)	Benign (N=42)		
Malignant	15 (60%)	5 (11.9%)	28.005	<0.001
Benign	10 (40%)	37 (88.1%)		

[Table/Fig-7]: Comparison of histopathology impression with LR 2.
*Total 70 patients were considered for the study. As three patients had borderline malignant in histopathology examination we did not consider them calculation of RMI, LR and IOTA and further comparisons

The sensitivity of LR-2 in predicting malignant histopathology was 76% (95% CI 54.87% to 90.64%), Specificity was 88.10% (95% CI 74.37% to 96.02%) [Table/Fig-8].

Parameters	Value	95% CI	
		Lower	Upper
Sensitivity	76.00%	54.87%	90.64%
Specificity	88.10%	74.37%	96.02%
False positive rate	11.9%	3.98%	25.63%
False negative rate	24.00%	9.36%	45.13%
Positive predictive value	79.17%	57.85%	92.87%
Negative predictive value	86.05%	72.07%	94.70%
Diagnostic accuracy	83.58%	72.52%	91.51%

[Table/Fig-8]: Predictive validity of LR-2 in predicting histopathology impression.

Among the malignant histopathology impression, 23 (92%) participants had malignant IOTA-simple rules and remaining 2(8%) participants had benign. Among the benign histopathology impression, 4 (9.52%) participants had malignant IOTA-simple rules and remaining 38 (90.48%) participants had benign. The difference in the proportion of IOTA-simple rules between histopathology impression was statistically significant (p-value <0.001) [Table/Fig-9].

The sensitivity of IOTA-simple rules in predicting malignant histopathology was 92% (95% CI 73.97% to 99.02%), specificity was 90.48% (95% CI 77.38% to 97.34%) [Table/Fig-10].

The CA-125 level had fair predictive validity in predicting malignant, as indicated by area under the curve of 0.773 (95% CI 0.655 to 0.891, p-value <0.001) [Table/Fig-11].

IOTA-simple rules	Histopathology impression		Chi-square	p-value
	Malignant (N=25)	Benign (N=42)		
Malignant	23 (92%)	4 (9.52%)	44.310	<0.001
Benign	02 (8%)	38 (90.48%)		

[Table/Fig-9]: Comparison of histopathology impression with IOTA- simple rules. *Total 70 patients were considered for the study. As three patients had borderline malignant in histopathology examination we did not consider them calculation of RMI, LR and IOTA and further comparisons

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	92.00%	73.97%	99.02%
Specificity	90.48%	77.38%	97.34%
False positive rate	9.52%	2.66%	22.62%
False negative rate	8.00%	0.98%	26.03%
Positive predictive value	85.19%	66.27%	95.81%
Negative predictive value	95.00%	83.08%	99.39%
Diagnostic accuracy	91.04%	81.52%	96.64%

[Table/Fig-10]: Predictive validity of IOTA-simple rules in predicting histopathology impression.

Test result variable(s)	Area under the curve	Asymptotic 95% Confidence interval		p-value
		Lower bound	Upper bound	
CA-125 level	0.773	0.655	0.891	<0.001

[Table/Fig-11]: Comparison of predictive validity of CA-125 level in predicting histopathology (Malignant).

DISCUSSION

A total of 70 women were included in the final analysis. Among the study population, 30% of the women had attained menopause. 70% of the women were premenopausal. In the study by Javdekar R and Maitra N 2015 [6], 58.5% were premenopausal and 41.5% of the women were postmenopausal. The mean CA-125 levels among the study population were 108.82 U/mL. There was a wide variability in the CA-125 levels ranging from as low as 5 U/mL to as high as 1000 U/mL. The median value was 18.90 U/mL which was much less than the mean, indicating that the distribution was right skewed [6]. In the study by Zurawski VR Jr et al., for assessing the utility of CA-125 in predicting ovarian cancer, the median level of CA-125 among the cases was 18 U/Ml [7]. In the study by Helzlsouer KJ et al., the median level of CA-125 at the time of diagnosis was 35.4U/mL which is higher than the current study [8]. In the study by Javdekar R and Maitra N, among those with benign tumours, the mean CA-125 levels was 33 U/mL and median CA-125 levels was 13 U/mL [6]. Among those who had malignant ovarian tumours, the mean CA-125 levels were 395 U/mL and the median CA-125 level was 329 U/mL.

The diagnostic accuracy of RMI 1 the present study is similar to that of the study by Karimi-Zarchi M et al., [Table/Fig-12] [9].

Study	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Current study	52%	90.48%	76.47%	76%	76.12%
Karimi-Zarchi M et al., (2015) [9]	75.43%	77.46%	57.30%	88.70%	76.88%

[Table/Fig-12]: RMI-1 predictive validity: comparison with other studies [9].

The overall diagnostic accuracy of RMI 2 was 77.6%. The diagnostic accuracy in this present study is comparable to the study by Karimi-Zarchi M et al., [9]. The sensitivity and PPV of this study are lower when compared to other studies [7-9]. The specificity of this study is comparable to the studies by Yamamoto Y et al., Javdekar R and Maitra N, van den Akker PA et al., Obeidat BR et al., 2004 and the specificity is lower compared to the study by Manjunath AP et al., [4,6,10-12]. The PPV is comparable to the study by Javdekar R and Maitra N and lower than the studies by Obeidat BR et al., Yamamoto Y et al., and Manjunath AP et al., [4,6,11,12]. The NPV is comparable to the study by Obeidat BR et al., and higher than the study by Manjunath AP et al., [11,12]. The NPV is lower than the studies by Javdkar and Maitra, Karimi-Zarchi M et al., and van den Akker PA et al., [6,9,10]. The comparisons are given in [Table/Fig-13].

Study	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Current study	60%	88.10%	75%	78.70%	77.60%
Javdekar R and Maitra N (2015) [6]	70.50%	87.80%	70.50%	87.80%	
Karimi-Zarchi M et al., (2015) [9]	79.36%	78.95%	58.44%	90.08%	78.93%
Manjunath AP et al., (2001) [12]	73.00%	90.00%	93.00%	66.00%	

[Table/Fig-13]: RMI-2 predictive validity: comparison with other studies [6,9,10].

The specificity of this current study is a little lower than the study by Sayasneh A et al., and higher than the study by Karimi-Zarchi M et al., [9,13]. There was also a very low false positive rate of 11.9%.

The sensitivity of RMI-3 was lower than RMI-2 at 52%. The sensitivity of this current study is much lower than the studies by Karimi-Zarchi M et al., and Sayasneh A et al., [9,13]. The PPV in the current study is higher and NPV is lower than the study by Karimi-Zarchi M et al., [9]. The diagnostic accuracy however is similar to the study by Karimi-Zarchi M et al., [9].

Similar to RMI 4, LR-2 was also found to be a good rule out test due to the high specificity of 88.10% and a low false positive rate of 11.90%. The specificity of RMI-1 to RMI-4 and LR-2 of this study is comparable to the study by Sayasneh A et al., and higher compared to Nunes N et al., Testa A et al., and Nunes N et al., [13-16]. However, the sensitivity was low at 76% and false negatives rate was high at 24%. The sensitivity of the current study is much lower compared to other studies by Nunes N et al., Sayasneh A et al., [13], Testa A et al., and Nunes N et al., [13-15,17].

Compared to RMI-1,2,3,4 and LR-2 models, IOTA model had the highest level of significant association with histopathological confirmation. The sensitivity of IOTA model in this current study is comparable to the studies by Kaijser J et al., (sensitivity 90%, specificity 93%), Nunes N et al., (the pooled sensitivity was 93% and the pooled specificity was 95%) and Garg S et al., (sensitivity 93% and specificity was 80%) [17-19]. The sensitivity is higher than the study by Tantipalakom C et al., (sensitivity 82.9%) and lower than the study by Testa A et al., (sensitivity 67%, specificity 91%) [15,20]. The specificity is higher than the studies by Testa A et al., and Garg S et al., (values were mentioned above) [15,19]. The specificity is lower than the studies by Kaijser J et al., Nunes N et al., 2014 and Tantipalakom C et al., [17,18,20]. The diagnostic accuracy of the current study is higher than the study by Garg S et al., [19].

CA-125 levels had a fair predictive value in predicting malignancy as indicated by a 77.3% area under the ROC curve. The area under curve for CA-125 according to the study by Mehri JS et al., was 63.3% [21]. Hence, comparing all scoring systems for predicting malignancy, IOTA-simple rules was found to have the highest level of sensitivity and specificity along with low false positive and false negative rates.

Limitation(s)

As, the sample size of the study was less multicentric studies with large sample size can be planned, for affirmative conclusions which can be accepted by the researchers across the world.

CONCLUSION(S)

Early diagnosis of ovarian cancer is crucial for timely management. In the current study population, only one-fourth were suspected to have malignant ovarian tumours. However, IOTA-simple rules were

found to be superior to LR-2 with the highest level of sensitivity and specificity. Hence, for early risk stratification of adnexal masses and for deciding the type of surgery, IOTA-simple rules can be used as a screening tool due to its high sensitivity, specificity, PPV, NPV and diagnostic accuracy. This would aid in better patient management, thereby reducing complications and improved survival.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Obstetrics and Gynaecology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Madhuranthagam, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. SR Ramya,
Assistant Professor, Department of Obstetrics and Gynaecology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Madhuranthagam, Tamil Nadu, India.
E-mail: amarnageshkumar@gmail.com

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