COMPARATIVE ASSESSMENT OF RMI-IV AND RMI-V IN PREOPERATIVE PREDICTION OF OVARIAN TUMOR TYPE IN PREGNANT WOMEN

Gerasimova AA[1], Chevchenko UV[1], Klimenko PA[2] ✉, Asyrafyan LA[3]

[1] Center of Family Planning and Reproduction of the Moscow Healthcare Department, Moscow, Russia

[2] Pirogov Russian National Research Medical University, Moscow, Russia

[3] V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia

Prediction of ovarian tumor type in pregnant women is of great clinical significance, however, it is vastly difficult. In the last 5–10 years gynecologists were suggested to use RMI (Risk of Malignancy Index) in non-pregnant women, however the value of the test for obstetric practice has yet to be established. The study was aimed to determine RMI-IV and RMI-V during preoperative non-invasive prediction of ovarian tumor type in pregnant women. Retrospective and prospective clinical and laboratory data of 114 pregnant women aged 20–38 were collected. Among them 15 patients had malignant ovarian tumors (MOTs), 28 had borderline ovarian tumors (BOTs), and 71 had benign ovarian tumors. Color Doppler and pulsed wave Doppler ultrasound was performed. The levels of CA-125 were defined by enzyme immunoassay. Models IV, V were used to assess the risk of ovarian cancer. A moderate non-significant increase in blood levels of CA-125 compared to patients with benign ovarian tumors and BOTs was found in pregnant women with MOTs. Patients with BOTs and MOTs showed higher RMI-IV and RMI-V values compared to the group of pregnant women with benign ovarian tumors. Extreme values are required to guarantee the differences in the diagnosis of tumors (RMI-IV > 3500 indicate the presence of MOTs, the values below 100 indicate no malignancy). Similar RMI-V values are 1500 and 60. However, in most cases, availability of RMI-IV and RMI-V is insufficient for decision making, and a comprehensive approach has to be used. Thus, it is difficult to define ovarian mass type in pregnant women using RMI only. Comprehensive clinical assessment with the use of imaging methods is required for preoperative prediction of ovarian mass type in pregnant women, along with the use of prognostic models taking into account the majority of descriptive “morphological” tumor characteristics.

Keywords: benign and malignant ovarian tumors, ultrasound, RMI

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Compliance with ethical standards: the study was approved by the Ethics Committee of Pirogov Russian National Research Medical University (protocol № 176 of 25 June 2018). All patients submitted the informed consent to study participation.

✉ **Correspondence should be addressed:** Pyotr A. Klimenko
Sevastolopsky prospect, 24a, Moscow, 117209, Russia; pa.klimenko@mail.ru

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СРАВНИТЕЛЬНАЯ ОЦЕНКА RMI-IV И RMI-V ПРИ ДООПЕРАЦИОННОМ ПРОГНОЗИРОВАНИИ ХАРАКТЕРА ОПУХОЛЕЙ ЯИЧНИКОВ У БЕРЕМЕННЫХ

А. А. Герасимова[1], Ю. В. Шевченко[1], П. А. Клименко[2] ✉, Л. А. Ашрафян[3]

[1] Центр планирования семьи и репродукции Департамента здравоохранения города Москвы, Москва, Россия

[2] Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва, Россия

[3] Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии имени В. И. Кулакова, Москва, Россия

Прогнозирование характера опухолей яичников у беременных имеет важное клиническое значение, но значительно затруднено. В последние 5–10 лет у небеременных в гинекологии предложено использовать RMI (Risk of malignancy index), однако в акушерской практике ценность этого исследования еще не установлена. Целью исследования было определить RMI-IV и RMI-V при дооперационном неинвазивном прогнозировании характера опухолей яичников у беременных. Ретро и проспективно отобраны данные клинико-лабораторного обследования 114 беременных 20–38 лет, из которых 15 пациенток имели злокачественные опухоли яичников (ЗОЯ), 28 пациенток — пограничные опухоли яичников (ПОЯ) и 71 пациентка — доброкачественные опухоли яичников (ДОЯ). Проводили ультразвуковое исследование (УЗИ) с использованием цветовой допплерографии и импульсноволновой допплерометрии. Определяли концентрацию СА-125 с помощью иммуноферментного анализа. Для оценки риска рака яичников использовали модификации IV, V. В крови беременных с ЗОЯ было выявлено умеренное статистически не значимое повышение СА-125 по сравнению с таковыми значениями у пациенток с ДОЯ и ПОЯ. По сравнению с группой беременных с ДОЯ, пациентки с ПОЯ и ЗОЯ демонстрировали повышенный уровень RMI-IV и RMI-V. Для гарантированного различия в диагностике опухолей необходимы краевые значения (RMI-IV — выше 3500 указывают на ЗОЯ, ниже 100 — на отсутствие злокачественного процесса). Для RMI-V аналогичными значениями являются 1500 и 60. Однако для принятия решения в большинстве наблюдений наличия только показателей RMI-IV и RMI-V было недостаточно и требовалось использовать комплексный подход. Таким образом, определить характер новообразований яичников у беременных трудно, если использовать только индексы RMI. Для дооперационного прогнозирования характера опухолей яичников у беременных требуется комплексное клиническое обследование с использованием визуализационных методов, применение моделей прогнозирования, учитывающих большое количество описательных «морфологических» характеристик опухолей.

Ключевые слова: доброкачественные и злокачественные опухоли яичников, ультразвуковое исследование, RMI

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✉ **Для корреспонденции:** Петр Афанасьевич Клименко
Севастопольский проспект, д. 24а, г. Москва, 117209, Россия; pa.klimenko@mail.ru

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Differential diagnosis of ovarian neoplasms in pregnancy, which are often treated using pelvic surgery, is of great scientific and practical interest. The increase in the standardized incidence rate of this disorder in Russia over the last 5 years is 4% [1]. There is a trend toward the increase in the number of cases of ovarian tumors (OT) associated with pregnancy [2]. However, 87.0% of young patients have benign tumors. The properly selected strategy (conservative treatment or surgery) is especially important in pregnant women. Strategy is selected based on the ovarian mass type defined by specific assessment methods [3–5]. As is known, there might be false negative and false positive results when forecasting. In obstetric practice, both type I (false positive, diagnosed disorder) and type II (false negative, the disorder is undiagnosed when there is a disorder) errors are unacceptable in patients with ovarian tumors. Type I errors may result in unreasonable surgical treatment of the tumor during early embryogenesis and placentation, as well as in possible loss of a desired pregnancy; without treatment type II errors may result in rapid disease progression.

The improvement of non-invasive ovarian tumor diagnosis methods based on the combination of clinical data, tumor marker levels and imaging techniques resulted in the proposed use of the Risk of Malignancy Index (RMI) for differential diagnosis of ovarian tumors [6]. It is believed that RMI are more informative in differential diagnosis performed in patients with ovarian masses compared to other criteria for malignant ovarian tumors [7]. To date, five RMI models are available. However, the use of those in gynecological practice is not always reliable due to lack of universality and ambiguous results, and there is too little obstetric research.

That is why the study was aimed to determine RMI-IV and RMI-V during preoperative non-invasive prediction of ovarian tumor type in pregnant women.

METHODS

In 2000–2021, retrospective and prospective clinical and laboratory data of 114 pregnant women aged 20–38 (median age 31.3 years) were collected. Among them 15 patients had malignant ovarian tumors (MOTs), 28 patients had borderline ovarian tumors (BOTs), and 71 patients had benign ovarian masses (Table 1). Inclusion criteria: early pregnancy (1^{st}–2^{nd} trimester) and ovarian tumor. Exclusion criteria: no pregnancy.

The study was performed in the Center of Family Planning and Reproduction of the Moscow Healthcare Department.

Transabdominal and transvaginal color Doppler and pulsed wave Doppler ultrasound was performed with the Voluson E8 scanner (General Electric; USA).

CA-125 levels were assessed by enzyme immunoassay using the test system by the manufacturer (Siemens; Germany).

The combined ovarian cancer (OC) risk assessment indicators (Risk of Malignancy Index, RMI) IV, V, were used to assess the risk of OC [8–11].

Statistical processing was performed in the SPSS 15.0 software package (INC; USA). Descriptive statistics and Spearman's rank correlation were used. The search for significant differences between samples was carried out using the Wilcoxon–Mann–Whitney test. The differences were considered significant at $p < 0.01$. Extreme values (series limits) limiting the variational series were presented as ($V_{max} \div V_{min}$). Descriptive statistics for quantitative variables was presented as M (SD) (mean and standard deviation). The method involving estimation of the area under the sensitivity vs. specificity curve (AUC) were used for ROC curve analysis. This method makes it possible not only to assess the diagnostic accuracy, but also to decide on a balance between type I and type II errors.

RESULTS

Epithelial tumors, mostly of benign histologic type, were diagnosed in the majority of pregnant women (n = 71). The share of malignant epithelial neoplasms (6 out of 15) was almost the same as that of germ cell tumors (7 out of 15). Serous tumors prevailed among BOTs (25 out of 28). Stage 1A BOTs and MOTs were identified in the majority of cases, however stage IIIC tumors were found in 7 patients. Distribution of OT histologic types in pregnant women is provided in Table 1.

The data obtained showed that all the surveyed pregnant women were through their fertile life period at almost the same age. Furthermore, a slight non-significant increase in blood levels of CA-125 compared to patients with benign ovarian masses and BOTs was found in pregnant women with MOTs (Table 2).

Patients with BOTs and MOTs showed higher RMI-IV and RMI-V scores compared to the group of pregnant women with benign ovarian tumors.

The case-by-case analysis showed that the highest RMI-IV (540–2888) and RMI-V (200–1444) values in the group of pregnant women with benign ovarian tumors were registered in patients with bilateral deep ovarian endometriosis. In patients with teratomas, RMI-IV varied between 8.3–256, while RMI-V was between 8.3–128. In patients with serous papillary cystadenomas, RMI-IV was within the range of 18.7–397, while RMI-V was between 18.7–198.6. The lowest RMI-IV (13–144) and RMI-V (13–72) values were found in patients with mucinous cystadenomas. In patients with other benign ovarian tumors, RMI-IV and RMI-V varied between the specified values. Both low and high RMI-IV (8.9–1776) and RMI-V (15–888) values were observed in patients with serous borderline tumors. Therefore, it was impossible to differentiate benign from malignant ovarian tumors based on the studied malignancy indices. In patients with MODs, RMI-IV varied between 123.2 and 5631, while RMI-V was within the range of 61.6–2815.6, these values exceeded that of patients with benign ovarian tumors in every third case. Significant differences were revealed in patients with stage IIIC MODs: RMI-IV in patient with yolk sac tumor was 1016, while RMI-V was 508; in patient with serous adenocarcinoma RMI-IV reached 5631.2, and RMI-V was 2815.6. Diagnostic algorithms also revealed high indicators in patients with stage IA dysgerminomas: RMI-IV between 1152–2168, RMI-V within the range of 567–1084.

Distribution of observation rates over the RMI-IV and RMI-V log10 scales shows intervals between the index values, in which the results of three groups overlap (Fig. 1). These values were 100 and 1200 for RMI-IV, while the values for RMI-V were 70 and 1200. It was impossible to define which group this or that tumor found in pregnant woman belonged to using RMI in this interval, that is why it was necessary to use additional examination methods in patients with RMI values between 70–1200. It was impossible to differentiate benign from borderline ovarian tumors based on the diagnostic models (RMI-IV, V).

DISCUSSION

The results of studies focused on using multimodality diagnostic systems indicate the dubious value of RMI for preoperative prediction of the ovarian mass type. This is primarily due to diverse morphological types and phenotypic heterogeneity of ovarian neoplasms. Therefore, one should not use RMI-IV and RMI-V only to predict the ovarian mass type, since prediction is essential for selection of management strategy in patients with OTs found during early pregnancy.

Table 1. Distribution of ovarian tumor histological types in pregnant women

1. Malignant ovarian tumors	
Epithelial	
Serous adenocarcinoma	3
Mucinous adenocarcinoma	2
Clear cell adenocarcinoma	1
Germ cell tumors	
Immature teratoma	2
Dysgerminoma	3
Yolc sac tumor	1
Mixed germ cell tumor	1
Metastatic tumors	2
Total:	15
2. Borderline ovarian tumors	
Serous adenocarcinoma	24
Mucinous adenocarcinoma	1
Endometrioid tumors	1
Serous and mucinous tumors	2
Total:	28
3. Benign ovarian tumors	
Struma ovarii	1
Serous cystadenoma	19
Mucinous cystadenoma	9
Thecoma/fibroma	6
Mature teratoma	16
Endometrioma	20
Total:	71

When trying to predict tumor types in pregnant women, we had to consider two adverse outcomes, thus bringing together type I and type II errors. In other words, the error was critically important for the final decision. This led to the fact that we could not sacrifice specificity (share of false-negatives) in favor of sensitivity and had to use diagnostic methods with maximum accuracy of 90% or more.

When trying to define the cutoff RMI-IV and RMI-V values, we managed to reach the accuracy of determining MOTs of 81%, however, such results were associated with low sensitivity (the number of diagnosed MOTs was lower that the true number of MOTs). With the cutoff values shift towards sensitivity we managed to achieve accuracy of 93% at the expense of the diagnosis of non-malignant tumors: in these

Table 2. Descriptive statistics of CA-125 and Risk of Malignancy indices (RMI-IV and RMI-V) in pregnant women with benign, borderline and malignant ovarian tumors

		Benign tumors	Borderline tumors	Malignant tumors
Number		71	28	15
CA-125	Value	69.7 ± 49.9	63.3 ± 52	95 ± 53.1
	Minimum	5.29	4.8	15.4
	Maximum	361	361	703
	Standard deviation	73.6	75.9	170.9
	Median	40	34.6	73.5
RMI-IV	Value	275.6 ± 56.1	283.3 ± 74.4	1031 ± 357.2
	Minimum	8.3	8.9	123
	Maximum	2888	1776	5631
	Standard deviation	505	393.7	1383.3
	Median	88	104	518.4
RMI-V	Value	125.0 ± 25.2	183.7 ± 42.0	515 ± 178.6
	Minimum	5.29	9.7	61
	Maximum	1444	888	2815
	Standard deviation	227	222.4	691.6
	Median	54	70	259.2

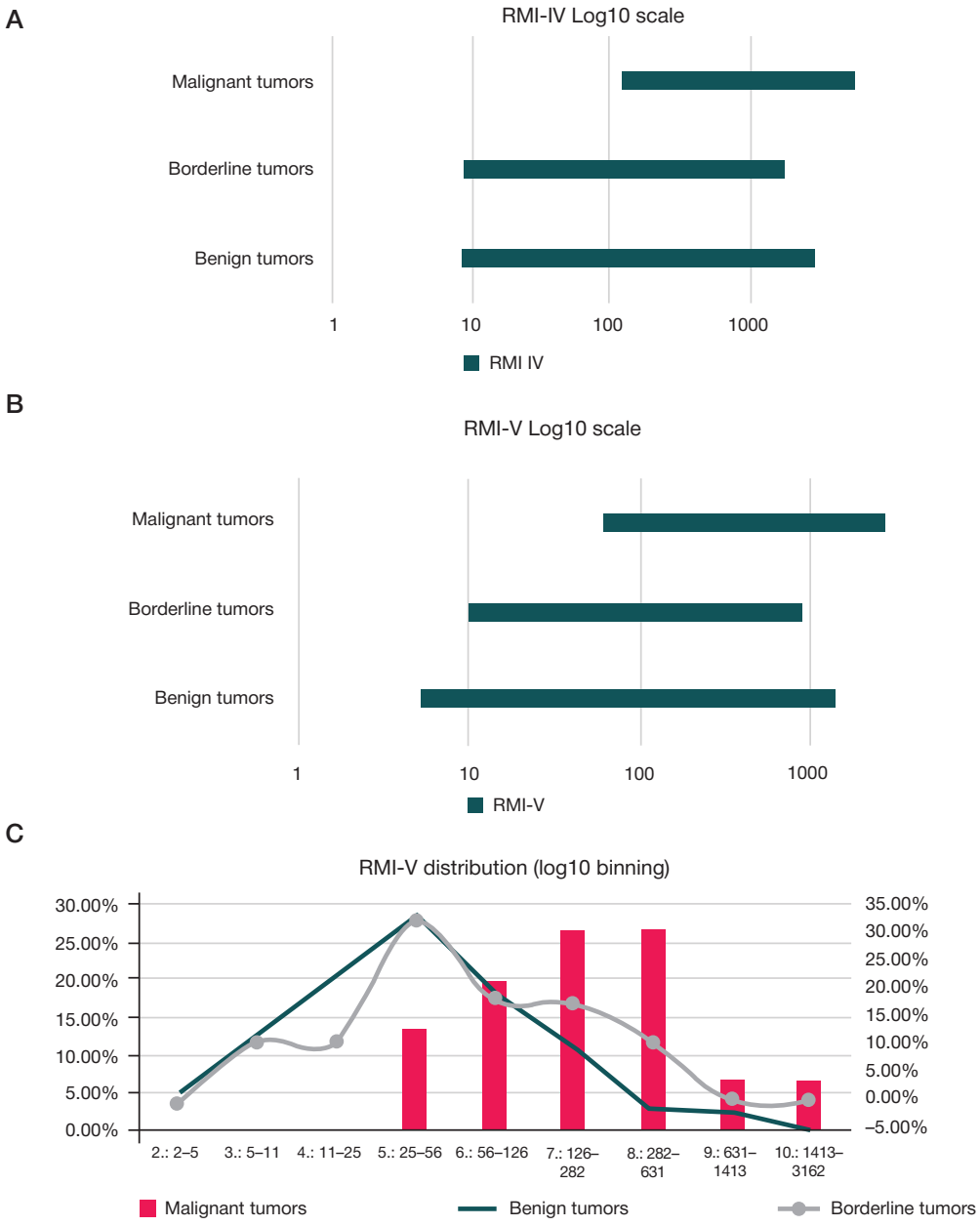

Fig. 1. Frequency analysis of RMI-IV and RMI-V in the surveyed pregnant women

cases accuracy dropped to 70%. Furthermore, 37% of false-positives (suspected MOTs in patients with no MOTs) were observed, which was considered unacceptable (Fig. 1 and 2).

With all the advantages of using RMI-IV and RMI-V, extreme values (series limits) of indices (RMI-IV > 3500 indicate the presence of MODs, RMI-IV below 100 indicate no malignancy) were needed to guarantee the differences in prognosis. Similar RMI-V values were 1500 and 60. Furthermore, lower values had greater significance based on the incidence rate. However, in the majority of cases RMI-IV and RMI-V availability was insufficient, and a comprehensive approach had to be used: ultrasound and MRI data had to be considered along with RMI values, as well as logistic regression models based on the analysis of multiple OT markers, such as earlier reported methods [12–18].

It was shown that RMI (I–III) values in patients with benign ovarian tumors should not be higher than 200, while RMI-IV in patients with MOTs should exceed 450 [11, 19]. Sensitivity was 73%, 81%, and specificity was 93.7%, 89.6%, 93.7%, 92.3%. According to these findings, proper diagnosis is possible in 95% of cases.

However, there are reports that sensitivity exceeds 90% and false negative rate is about 10% in all RMI models when predicting the ovarian mass type [20]. It has been found, though, that RMI-IV is ineffective for prediction of tumor type, even the threshold value of 450. Furthermore, the need to use Doppler techniques, that was later factored in the algorithm together with RMI-V, was substantiated in predicting. Parameters of tumor blood flow, Doppler ultrasound blood flow parameters, and the presence of solid component were malignancy predictors, unlike tumor size and isolated levels of CA-125.

When using RMI-IV, other researchers observed false positive results in non-pregnant patients with benign ovarian tumors: endometrioid cystadenomas, fibromas, serous cystadenofibromas [21]. False negative results were registered in patients with MOTs (clear cell and mucinous carcinomas).

According to other sources, RMI < 25 indicates low risk of malignancy, 25–200 indicates moderate risk, while the levels exceeding 200 may confirm high risk of malignant ovarian

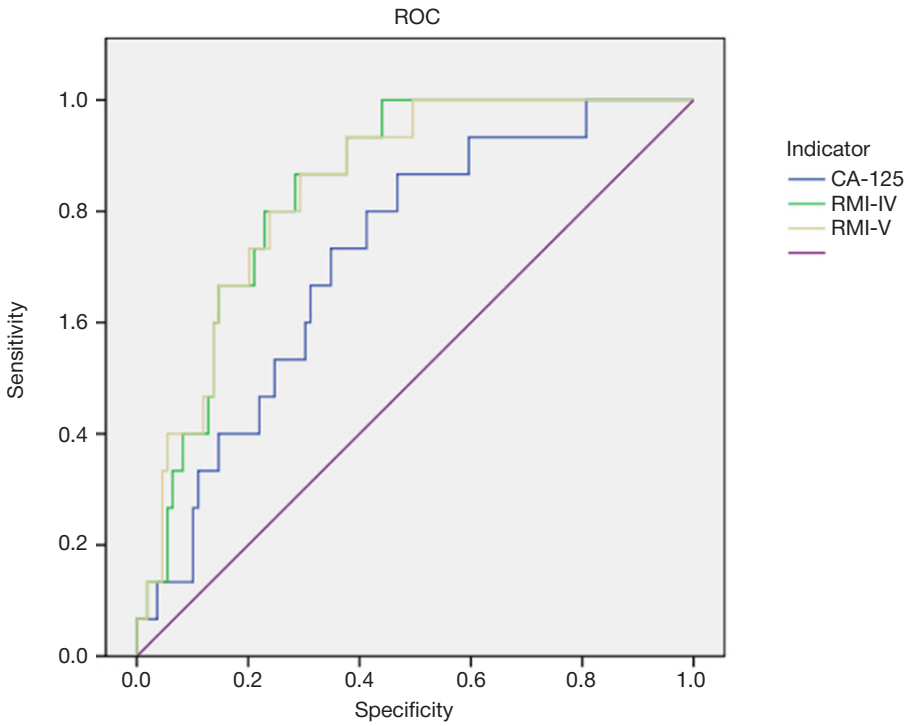

Fig. 2. ROC-curves characterizing sensitivity and specificity of CA-125, RMI-IV and RMI-V as predictors of the successful diagnosis of malignant ovarian tumors in pregnant women

lesion [22]. However, high RMI values have been diagnosed in patients with deep ovarian endometriosis, and low values (< 200) have been found in patients with clear cell carcinoma.

The results reported in the paper showing that RMI should not be used solo during pregnancy due to low sensitivity (50–55.6%) are most similar to our results. Conclusions about benign ovarian tumors, BOTs and MOTs should be drawn based on RMI in combination with clinical features and the results of imaging tests [23].

CONCLUSIONS

It is difficult to define ovarian mass type in pregnant women using RMI only. Comprehensive clinical assessment with the use of imaging methods is required for preoperative prediction of ovarian mass type in pregnant women, along with the use of prognostic models taking into account the majority of descriptive “morphological” tumor characteristics.

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