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Triaging Women with Pregnancy of Unknown Location: Evaluation of Protocols Based on Single Serum Progesterone, Serum hCG Ratios, and Model M4

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Abstract

Background: The purpose of the current study was to evaluate the ability of three protocols to triage women presenting with pregnancy of unknown location (PUL).

Methods: Women with pregnancy of unknown location were recruited from Aziz Medical Centre from 1st August, 2018 to 31st July, 2020. The criterion of progesterone, human chorionic gonadotrophin (hCG) ratio, and M4 algorithm were used to predict risk of adverse pregnancy outcomes and classify women. Finally, 3 groups were established including ectopic pregnancy, failed pregnancy of unknown location, and intrauterine pregnancy (IUP). The primary outcome was to assign women to ectopic pregnancy group using these protocols. The secondary outcome was to compare the sensitivity and specificity of the three protocols relative to the final outcome.

Results: Of the 288 women, 66 (22.9%) had ectopic pregnancy, 144 (50.0%) had intrauterine pregnancy, and 78 (27.1%) had failed pregnancy of unknown location. The criterion of progesterone had a sensitivity of 81.8%, specificity of 27%, negative predictive value (NPV) of 83.3%, and positive predictive value (PPV) of 25% for high risk result (ectopic pregnancy).The hCG ratio had sensitivity of 72%, specificity of 73%, NPV of 90%, and PPV of 44% for high risk result (ectopic pregnancy). However, model M4 had sensitivity of 86.4%, specificity of 91.9%, NPV of 95.8%, and PPV of 76% for high risk result.

Conclusion: Based on the findings of the study, it was revealed that prediction model of M4 had the highest sensitivity, specificity, negative predictive value and positive predictive value for high risk result (ectopic pregnancy).

Keywords: Ectopic pregnancy, Miscarriage, Prediction model, Pregnancy of unknown location, Resource allocation, Triage methods, Triage standards, Ultrasonography.
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Introduction

Pregnancy of unknown location continues to be an area of concern (1). This concern is magnified when a woman conceives after fertility treatment. The clinician is in a dilemma because the patient has a positive pregnancy test but the location of pregnancy cannot be determined and counselling becomes extremely difficult. The parents-to-be are in a grey area whether to celebrate or be anxious about the outcome (2). Ultrasound is a necessary tool to evaluate preg-

nancy of unknown location which is basically a condition and not an actual diagnosis. The differential diagnosis ranges from intrauterine pregnancy, failed pregnancy, and ectopic pregnancy. There is still lack of evidence and a variety of models, ratios, and markers have been suggested to aid in follow-up strategies (3). Management protocols incorporate biomarkers, *i.e*. progesterone and human chorionic gonadotropin (hCG), but no consensus is present at the moment.

Progesterone is a good predictor of a viable pregnancy but not the location of pregnancy which is of utmost importance. A threshold level of 10 *nmol/L* has been proposed for pregnancies, but this approach classifies most pregnancies as high risk and a triage becomes difficult (4).

Serum hCG in conjunction with ultrasound of pelvis is the most commonly employed marker for evaluating pregnancy of unknown location. However, a single measurement is not sufficient to diagnose and can be falsely reassuring. Moreover, this approach is invariably unhelpful in excluding the presence of an ectopic pregnancy (5). HCG ratio is defined as the 48-*hr* hCG level divided by the initial (0-*hr*) hCG level (6-8). M4 is a logistic regression model based on the initial serum hCG and the hCG ratio as variables (9). This model was found to be superior in performance to a single progesterone cut-off of <10 *nmol/L* or the hCG ratio alone.

The model did much better in the European population but the results from American population were not convincing (10). Since pregnancy of unknown location is a classification and not a diagnosis, the strategies to effectively manage the condition continue to evolve. This research was performed to assess three commonly used protocols for screening pregnancy of unknown location in a Pakistani cohort. The aim of this study was to evaluate the ability of protocols to classify women presenting with pregnancy of unknown location as having ectopic pregnancy.

Methods

Pregnant women, aged 20 to 39 years and receiving ovulation induction, were recruited for this study from infertility clinic at Aziz Medical Centre in Karachi, Pakistan, from 1st August, 2018 to 31st July, 2020.

Pregnancy was defined as positive urine pregnancy test and an amenorrhea of 6 weeks. A pregnancy of unknown location was defined if no intrauterine or extra uterine pregnancy was seen on the first transvaginal scan (1).

All women with PUL were included if they were clinically stable and complied with follow- up. Those who did not have the pregnancy test (Beta-hCG) at 48 *hr* were also excluded. Those who conceived after in vitro fertilization or intrauterine insemination were excluded as well.

After obtaining written and informed consent, all women who met the inclusion criteria comprised the study participants. The study protocol was explained and an emergency contact number was given to all women. Regarding the sample size, it was assumed that if 20% of the subjects in the population with pregnancy of unknown location had ectopic pregnancy, the study would require a sample size of 246 women. The sample size was inflated by 20% to compensate for deviation from the protocol.

Initial serum hCG and serum progesterone measurement was done for women labelled as PUL. They were then advised to have a repeat serum HCG measurement. For estimation of serum hCG and serum progesterone levels, all selected blood samples of subjects were drawn by venipuncture in serum separator tubes. Serum hCG levels were determined by enzyme-linked immunosorbent assay (ELISA), using hCG kit.

The criterion of hCG ratio: The hCG ratio was calculated by dividing the hCG level at 48 *hr* by initial hCG. The patient was classified as 'high risk for ectopic pregnancy' if the ratio was between 0.87 and 1.66. In this case, the woman was called for immediate transvaginal ultrasound (TVS) by consultant gynaecologist and further hCG measurements. If the ratio was 0.87 or lower, the patient was classified as having failed pregnancy (6-8). Such patients were asked to have a third serum hCG test on day 7; if the levels had a decreasing pattern, they were advised to carry out a urine pregnancy test 2 weeks later. If the hCG ratio was 1.66, the patients were brought back for a further TVS in 7 days to confirm pregnancy location and viability. All pregnancies were followed up until the final outcome of the pregnancy was known.

The criterion of progesterone level: A woman was classified as "high risk" if the serum progesterone level was greater than 10 *nmol/L* and "low risk" if the level was less than 10 *nmol/L*.

The prediction model M4: For prediction model

M4, an excel sheet with the algorithm for prediction was installed in the Microsoft office which was freely accessible to all doctors. A woman with PUL had an initial hCG level measurement which was entered into the file. After 48 *hr*, another level was measured and subsequently entered into the same file that gave an estimation of risk. A woman was classified as "high risk" if the chance of ectopic pregnancy was greater than 5% and "low risk" if chance of ectopic pregnancy was less than 5%. The low risk category was further stratified as 1) risk of failed PUL (FPUL) >risk of IUP (low risk, probable FPUL) and 2) risk of IUP >risk of failed PUL (low risk, probable IUP). Those likely to have IUP underwent TVS after 1 week and those likely to have FPUL had a urine pregnancy test in two weeks (11). All participating doctors were explained beforehand that the model would serve just as a guide and it should not be blindly followed and management would depend on clinical situation.

Follow-up and categorization of outcome: All pregnancies were followed vigilantly and final outcome of each PUL was described as follows: 1) failed PUL, if serum hCG dropped to 10 or below or a urine pregnancy test was negative; 2) ectopic pregnancy, if ectopic pregnancy was seen on TVS or at laparoscopy and also if patients had static hCG levels (15% change over 48 *hr* for three consecutive occasions); and 3) IUP, if diagnosed using TVS on the basis of the visualization of an intrauterine gestational sac with or without a yolk sac or fetal pole or heterogeneous tissue in the uterine cavity consistent with retained products of conception.

A proforma was used to collect the data. The demographic data included age, height, weight of women, and area of residence. The findings on initial scan and hCG levels on presentation and 48 *hr* later were recorded. Serum progesterone and hCG ratios were also calculated.

The primary outcome measure in this study was to assign women with pregnancy of unknown location to ectopic pregnancy group after the initial screening using these criteria. The secondary outcome measure was to compare the sensitivity and specificity of the three criteria including progesterone, hCG ratio, and model M4 relative to the final outcome. The final outcome for this analysis was stratified into low risk result and high risk result. Low risk result was either a failed pregnancy or intrauterine pregnancy, and high risk result was an ectopic pregnancy.

All participants provided informed consent. The study was approved by ethics committee of the institute (IEC/AZIZ/11232) and Helsinki's declaration was followed. Furthermore, no subjects were harmed and confidentiality was maintained.

Statistical analysis: Shapiro Wilk test was used to assess normality of data distribution. The quantitative variables including age, duration of infertility, hCG level on presentation and 48 *hr* later, serum progesterone, and body mass index were presented by mean and standard deviation. One-way ANOVA was used to compare the groups. Frequency and percentages were computed for qualitative variables including the type of infertility, bleeding, pain, indication of scan, and history of ectopic pregnancy. Chi square test and Fisher's exact test were used to compare these variables at $p<0.05$.

A 2×2 contingency table was used to assess sensitivity, specificity, and positive predictive value and negative predictive value of all criteria relative to final outcome. The final outcome for this analysis was stratified into low risk and high risk results. SPSS software *vs.* 15.0 (IMB, USA) was used for all statistical analysis.

Results

During the study period, 314 women had PUL and were assessed for inclusion. Among them, 14 refused to participate, 7 women were lost to follow up, and 5 women refused to repeat hCG. Therefore 288 women were included.

Of these 288 women, 66 (22.9%) had ectopic pregnancy, 144 (50.0%) had IUP, and 78 (27.1%) had failed PUL on their follow-up. When stratified according to final outcome, the women with PUL were similar in terms of age, bleeding, pain, and duration of subfetrility (Table 1). However, women with ectopic pregnancies had significantly different initial hCG level and hCG ratios and therefore required more blood tests and scans before final diagnosis.

The progesterone criterion classified 120 cases (41.7%) of ectopic pregnancy, 105 (36.5%) of IUP, and 63 (21.9%) of FPUL. The criteria correctly predicted 36/66 of ectopic pregnancies, 66/78 of FPUL, and 60/144 of IUP. This further implied that when progesterone criteria labelled a case as ectopic pregnancy, it was the correct diagnosis in only 30% of the cases (Table 2).

The criterion of hCG ratio classified 108 cases (37.5%) as ectopic pregnancy, 108 (37.5%) as IUP, and 72 (25.0%) as FPUL. The criteria correctly

Table 1. Characteristics of patients stratified according to groups

Characteristics		Ectopic pregnancy (n=66)	Intrauterine pregnancy (IUP) (n=144)	Failed pregnancy of unknown location (FPUL) (n=78)	p-value
		Mean standard deviation	Mean standard deviation	Mean standard deviation	
Age (years)		28.18±4.88	27.46±4.51	27.08±5.22	0.379
Infertility duration (years)		3.91±1.87	3.88±1.82	3.23±2.04	0.034
Human chorionic gonadotrophin initial value		1481.23±454.06	1485.63±439.68	1256.58±450.56	0.001
Human chorionic gonadotrophin value after 48 *hr*		1668.95±598.28	2802.01±1096.82	734.44±426.20	0.001
hCG ratio		1.17±.36	1.87±.46	.58±.23	0.001
Progesterone in *ng/ml*		22.09±11.98	44.79±15.96	9.31±6.08	0.001
Number of scans before diagnosis		3±1	2±0	3±0	0.001
Number of blood tests before diagnosis		3±0	2±0	2±0	0.001
Pain	Yes	18(27.3%)	42(29.2%)	27(34.6%)	0.588
	No	48(72.7%)	102(70.8%)	51(65.4%)	
Bleeding	Yes	33(50.0%)	87(60.4%)	45(57.7%)	0.365
	No	33(50.0%)	57(39.6%)	33(42.3%)	
Indication of scan	Bleeding	24(36.4%)	45(31.3%)	18(23.1%)	0.001
	Pain	9(13.6%)	0(.0%)	0(.0%)	
	Previous history of ectopic pregnancy	6(9.1%)	21(14.6%)	9(11.5%)	
	Reassurance	6(9.1%)	0(.0%)	0(.0%)	
	Previous miscarriage	6(9.1%)	18(12.5%)	12(15.4%)	
	Uncertain dates	6(9.1%)	18(12.5%)	12(15.4%)	
	Bleeding and pain	9(13.6%)	42(29.2%)	27(34.6%)	
History of ectopic pregnancy	Yes	6(9.1%)	21(14.6%)	9(11.5%)	0.001
	No	60(90.9%)	123(85.4%)	69(88.5%)	

†chi square test, Fisher's exact test or one-way ANOVA

Table 2. Cross tabulation of individual criteria with actual fate

Progesterone criterion	Final result at conclusion of follow-up			Total
	Ectopic	IUP	FPUL	
Ectopic pregnancy	36	72	12	120
Intrauterine pregnancy	3	60	0	63
Failed pregnancy of unknown location	27	12	66	105
Total	66	144	78	288
hCG ratio criterion				
Ectopic pregnancy	48	45	15	108
Intrauterine pregnancy	9	99	0	108
Failed pregnancy of unknown location	9	0	63	72
Total	66	144	78	288
Model M4				
Ectopic pregnancy	57	12	6	75
Intrauterine pregnancy	9	129	3	141
Failed pregnancy of unknown location	0	3	69	72
Total	66	144	78	288

* IUP= Intrauterine pregnancy, FPUL= Failed pregnancy of unknown location, hCG=Human Chorionic Gonadotrophin

Table 3. Cross tabulation of result risk with individual criteria

	Result risk		Total
	High risk (ectopic pregnancy)	Low risk	
Progesterone			
High risk	54 (81.8)	162 (73.0)	216 (75.0)
High risk	12 (18.2)	60 (27.0)	72 (25.0)
hCG			
High risk	48 (72.7)	60 (27.0)	108 (37.5)
Low risk	18 (27.3)	162 (73.0)	180 (62.5)
Model M4			
High risk	57 (86.4)	18 (8.1)	75 (26.0)
Low risk	9 (13.6)	204 (91.9)	213 (74.0)

* hCG=Human Chorionic Gonadotrophin

predicted 48/66 cases of ectopic pregnancy, 63/78 of FPUL, and 99/144 of IUP. When criterion of hCG ratio labelled a case as ectopic pregnancy, it was the correct diagnosis in only 44% of the cases (Table 2).

The M4 algorithm classified 141 cases (49.0%) as IUP, 75 (26.0%) as ectopic pregnancy, and 72 (25.0%) as FPUL. The criterion correctly predicted 57/66 cases of ectopic pregnancy, 69/78 of FPUL, and 129/144 of IUP. When criterion of M4 model labelled a case as ectopic pregnancy, it was the correct diagnosis in 76 % of the cases (Table 2).

When assessing the risk associated with PUL, the criterion of progesterone had a sensitivity of 81.8%, specificity of only 27%, NPV of 83.3%, and PPV of 25% for high risk result (ectopic).The hCG ratio had sensitivity of 72%, specificity of 73%, NPV of 90%, and PPV of 44% for high risk result (ectopic). Moreover, the model M4 had sensitivity of 86.4%, specificity of 91.9%, NPV of 95.8%, and PPV of 76% for high risk result (ectopic pregnancy) (Table 3).

Discussion

In our study, one fifth of women with PUL had an ectopic pregnancy. Our study shows that the prediction model M4 had the highest sensitivity, specificity, NPV, and PPV for a high risk result (ectopic pregnancy).

Our analysis is the first to assess the utility of three commonly used criteria for screening pregnancy of unknown location. Model M4 was applied in this study which has shown conflicting results with different populations due to protocol deviations. In the current research, the protocol was followed and two beta hCG samples were taken at 48 *hr*. However, the generalization of results is a vexing problem due to single centre design of the study.

Although the value of ultrasound in evaluating pregnancy of unknown location cannot be sufficiently emphasized, many algorithms have been developed to ensure a desired and wanted pregnancy. Clinicians should keep current with the utility of different clinical criteria that help assess the fate in controversial cases (11, 12). In this study, three of these criteria were assessed and it was found that the mathematical model using logistic regression analysis fares much better than the criterion of progesterone and hCG ratio. Our results are similar to other studies in which the mathematical model was utilized (11, 12). A recent meta-analysis showed that model M4 is the best available method to predict outcome of ectopic pregnancy (13). Our results are in agreement with the results of that analysis.

Serial beta hCG test is done to assess the fate in most set-ups; however, there have been instances where a pregnancy could not be visualized even at high levels and with a transvaginal scan (14). Transvaginal scan has better resolution and allows clear identification in many cases. The Royal College of Obstetricians and Gynaecologists has now declared transvaginal scan to be as reliable as the previous gold standard laparoscopy. However, in some cases, the pregnancy is not visualized at the mentioned cut off and may take time to be detected on a scan. The criteria come in handy in such cases, but all criteria are not sensitive enough or

sensitive in all populations.

The hCG protocol has been most widely used and is available in most set-ups. In our study, it had a high negative predictive value but a low positive predictive value. Therefore, there is room for refining and validating results in this regard. Our findings are in agreement with previous reports on the subject (15).

With respect to progesterone protocol, it has been previously established that hCG ratio should be preferred over progesterone level to predict viability of a pregnancy (16). The progesterone protocol in this study was used to further assess if the results would be different in our population. Recently, M6 model was evaluated and it revealed best sensitivity in diagnosing PUL (17). M6 model was not applied in our study and therefore the utility of that model cannot be assessed.

The ultrasonographer is a valuable member of the team in early pregnancy assessment procedures and proper triage involves evaluation of such pregnancies for several times. The evolving picture can be understood much better if all members are aware of the follow-up as pregnancy of unknown location requires triage.

In our study, model M4 was validated on a Pakistani cohort. The model performed much better than the other two criteria. The sensitivity of ectopic pregnancy in the current population was 86.5% which is in contrast to the data obtained in American studies (50%). The sensitivity of our population was even better than the one in UK which was 81%. Mathematical models cannot be directly relied upon in clinical settings. The models need to be validated in different populations and ongoing clinical surveillance is crucial.

The model has also been validated in Australian population and the results were convincing (18); in fact, it is a valuable tool to rationalize management in cases of pregnancy of unknown location.

However, the model provides an essentially useful tool for triaging these pregnancies. Women with low risk pregnancies receive fewer scans and blood tests. In a country where healthcare is expensive, such strategy can be very useful. Additionally, follow-ups can be tailored, so that women with higher risk are given priority and healthcare systems are not burdened.

Moreover, carefully selected women with low risk of ectopic pregnancy can also be reassured in the light of the obtained results. Pregnancy of unknown location can be a mentally taxing experience for the future parents.

A recent study has reported that model M4 shows a low discrimination capacity in classifying pregnancies as low- or high-risk for ectopic pregnancy in women who conceive after assisted reproductive techniques with low beta hCG levels (19). Our study included women who underwent ovulation induction; however, women undergoing IVF or IUI were not included. Therefore, our study cannot provide further insight into the claims made by this paper though the performance of the model was much better than the other two criteria in women undergoing ovulation induction. In another study, only 2% adverse pregnancy related events, secondary to the use of prediction model M4 was reported. The model is therefore safe as well as effective for triaging cases of PUL. The major limitation of the model is that the two beta hCG tests should be taken within 48 *hr* to be reliable. Similarly, in this study, included cases were advised to take the tests within 48 *hr*. This may explain the better sensitivity in our cohort.

Conclusion

Based on the findings of the study, it was revealed that prediction model M4 had the highest sensitivity, specificity, negative predictive value and positive predictive value for high risk cases of ectopic pregnancy in Pakistani cohort; nevertheless, the value of follow-up procedure for patients besides triage cannot be ignored. Moreover, the follow-up can be optional for low risk cases.

Conflict of Interest

None.

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