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THE DETERMINATION OF VARIOUS OUTCOMES OF THE PREGNANCY OF UNKNOWN LOCATION AND ITS CHOICE OF MANAGEMENT

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Abstract:

Objective: *The research objective is to determine the outcome of pregnancy of unknown location of cohort women treated in a tertiary-care hospital.*

Methods: *We conducted this prospective study at Services Hospital, Lahore (January 2017 to February 2018). We collected data for women with a history of bleeding/pain, amenorrhoea, and early pregnancy. The selected women underwent trans-vaginal ultrasonography once every week and beta-human chorionic gonadotropin levels two times every week. We did expectant management (EM) for failing PoUL and medical/surgical management for ectopic pregnancy and persistent PoUL.*

Results: *Out of 7215 patients, we found 30.60% (2212) with early pregnancy. The sample size was 2.53% (183) as these patients fulfilled inclusion criteria. The number of patients presented with amenorrhoea, bleeding, and the pain was 71.6% (131), 49.2% (90), and 50.8% (93) respectively. At the outcome, the number of failing PoUL, intrauterine pregnancy, ectopic pregnancy, and persistent PoUL was 54.6% (100), 31.7% (58), 7.7% (14), and 6% (11) respectively. We treated patients of persistent PoUL (All) and EP (05 or 36%) immediately. We managed the EP patients (05) surgically.*

Conclusions: *The choice of management for asymptomatic patients with PoUL is EM. The suspicion rate of persistent PoUL and EP was higher among patients for which, medical management is a better choice.*

Keywords: *Pregnancy of Unknown Location (PoUL), Ectopic Pregnancy (EP), Expectant Management (EM), Ectopic Pregnancy (EP), Discriminatory Zone (DZ), Surgical Management (SM), and Medical Management (MM).*

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INTRODUCTION:

PoUL is a term describing a woman with pregnancy test positive having no visuals of pregnancy on TVS (Trans-vaginal ultrasonography) [1]. The rate of incidence of PoUL is (8-to-10%) but some studies reported it to be (8-to-31%) [2]. PoUL has 4 different outcomes i-e failing PoUL, IUP (Intrauterine pregnancy), Persistent PoUL, and Ectopic pregnancy [3]. The common most outcome is failing PoUL with (44%-69%) rate where (7%-20%) with change into EP subsequently. There must be a balance between EP diagnosed late and possible IUP treated overly. Late diagnose of EP can cause mortality, morbidity, or can affect woman's fertility in future. We can measure the outcome of PoUL by measuring ultrasonography and β-hCG (beta-human chorionic gonadotropin) hormone [4]. Using single-value hCG serum has limited value in PoUL outcome prediction [5]. Evaluations are available about the concept of using serum-β-hCG with ultrasonography using DZ. It denotes β-hCG clear levels thus making gestational sac up to 100% visible on ultrasonography [3]. Using high-resolution TVs, researchers use (1000-2400 IU/L) discriminatory level of serum-β-hCG [2]. The serum-β-hCG level going above a certain discriminatory level with no visual of IUP leads to the assumption of having an EP. The performance of TVS must be meticulous so that image pitfall must not lead to wrong interpretation leading to false outcomes [2]. We can predict the PoUL outcome using β-hCG in addition to serum-progesterone [1]. A meta-analysis shows above (25 nmol/L) level of serum-progesterone association with non-viable pregnancy. However, (< 15.90 nmol/L) initial level reports being a viable pregnancy (0.30%). The level of serum-progesterone (<20 nmol/L) in the presence of PoUL predicts quick pregnancy resolution with sensitivity and specificity as 93% and 94% respectively. Level of (>25 nmol/L) and (>60 nmol/L) likely and strongly indicates IUP respectively [2]. The level of β-hCG also helps in PoUL following outcomes. In a normal viable pregnancy, β-hCG level increases more than 66% in two days but in 15% of normal pregnancies, the β-hCG doubling time is abnormal. Similarly (13%-21%) EP behave like IUP [3,6,7]. Other hormones are non-specific like CK (Creatinine Kinase) and CA-125 (Cancer Antigen-125). The CA-125 ratio at 0 and 48-hour is able to distinguish failing PoUL from IUP [8]. Non-specific Activin-A and Inhibin-A predict the PoUL outcome [1]. To predict a pregnancy outcome, protocols have used different diagnosis algorithms. PoUL can get conservative treatment or may need medically treated in the case of persistent PoUL. Surgical management is the option for symptomatic patients or changed to EP. MM with methotrexate has proved successful in asymptomatic persistent PoUL [9, 10].

SUBJECTS AND METHODS:

We conducted this prospective study at Services Hospital, Lahore (January 2017 to February 2018). After taking approval from the Institutional Review Committee, we took written consent from each patient and gave them a sheet of information about PoUL, treatment options, possible outcomes, and need to follow up. We included patients with bleeding/pain or amenorrhoea. We investigated these patients with TVS and serum-β-hCG. We took the DZ for β-hCG at (1500 IU/L) level. In ruling out IUP, adnexal mass, free fluid in a cul-de-sac, including EP, TVS proved useful. We excluded haemodynamically unstable patients. We recorded relevant data (keeping EP risk factors in mind) about patients on a pre-designed Pro-forma. To monitor the results, we followed-up all patients by clinical assessment, TVS, and serial β-hCG. We managed each patient with compliance, clinical assessment and their wish. We treated the patients of PoUL with β-hCG values decreasing with EM. We followedup this patient once and twice a week for TVs and β-hCG respectively. We treated patients with 03 βhCG values at a plateau, complaint, and stable haemo-dynamically with MM. MM included methotrexate (1 mg/kg) given IM (Intra-Muscularly) after ensuring no peptic-ulcer disease, active pulmonary disease, co-existent IUP, immune-deficiency, breastfeeding, and hypersensitivity to methotrexate. We admitted medically managed patients for 2-to-3 days as per clinical assessment and social needs. We follow-up the MM patients at day-one, four, and seven for signs/symptoms and βhCG values. We considered fall of (≤15%) β-hCG value at seventh day from day-first as successful outcome, otherwise, we discussed a second injection with the patient. We considered SM for patients non-compliant, unstable haemo-dynamically, refused methotrexate injection or failed to recover through MM. We admitted these patients treated them with laparoscopy/laparotomy and salpingostomy/salpingectomy as-per clinical assessment requirement. We collected data on a pro-forma analysing various parameters using percentages, frequencies, and mean ± SD as-per requirement.

RESULTS:

In our study, out of 7215 patients, only 30.6% (2212) had an early pregnancy. We labelled 2.76% (199) patients with/without symptoms as PoUL. There were 8% (16) patients that we lost their files during analysing data or got lost in follow-up. We had 92%

(183) patients as the final sample size. We divided them into 4 groups based on their outcome. The number of young patients (17-35 years' age) was 85% (155). The number of patients having (4-6) and 7 weeks of gestational age was 96% (177) and 3.80% (07) respectively. The number of patients presented with amenorrhea, bleeding, and the pain was 71.60% (131), 49.20% (90), and 50.80% (93) respectively. A total number of patients with EP was 6% (11), among them 73% (8) patients belonged to failing PoUL sub-group. The number of patients diagnosed with EP having adnexal-mass appeared was 7.70% (14). The number of patients with decreased β-hCG level was 28.5% (04) where EM resolved EP. The number of patients MM with methotrexate after contraindications ruled out was 36% (05). To resolve EP among these 5 patients, 80% (04) received single while 20% (01) received three doses. We managed 36% (05) patients of EP outcome surgically due to unsuitability of MM having high levels of β-hCG or being symptomatic. Among them, 80% (04) underwent laparoscopic-salpingectomy and 20% (01) had laparoscopicsalpingostomy. The number of patients with persistent PoUL was 6% (11) who were medically managed (100% resolved outcome) with methotrexate (single injection).

Table – I: Outcome of PoUL (183)

Outcome	Number	Percentage
Ectopic	14	7.7
Failing PUL	100	54.6
Intrauterine Pregnancy	58	31.7
Persistent PUL	11	6.0

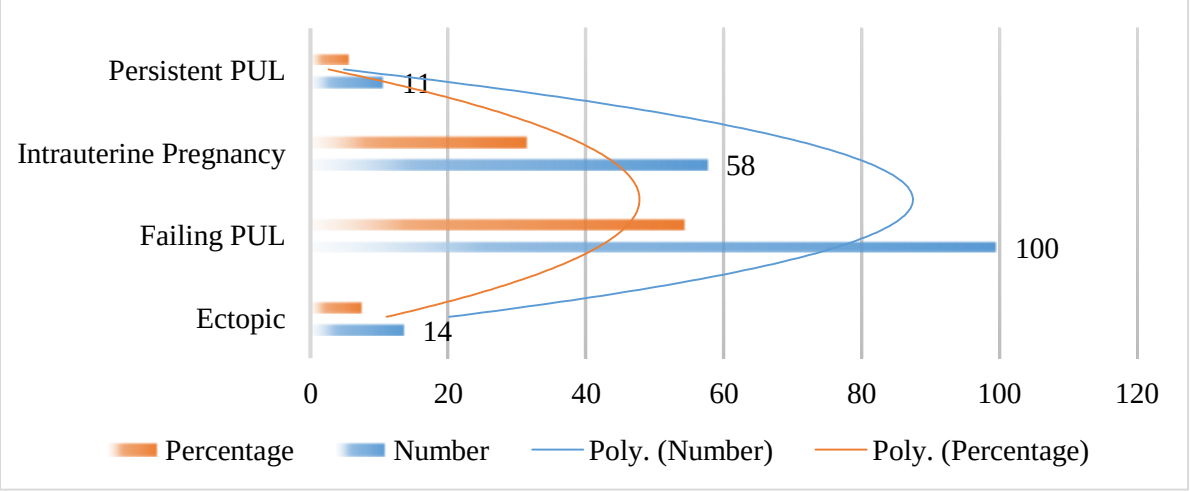
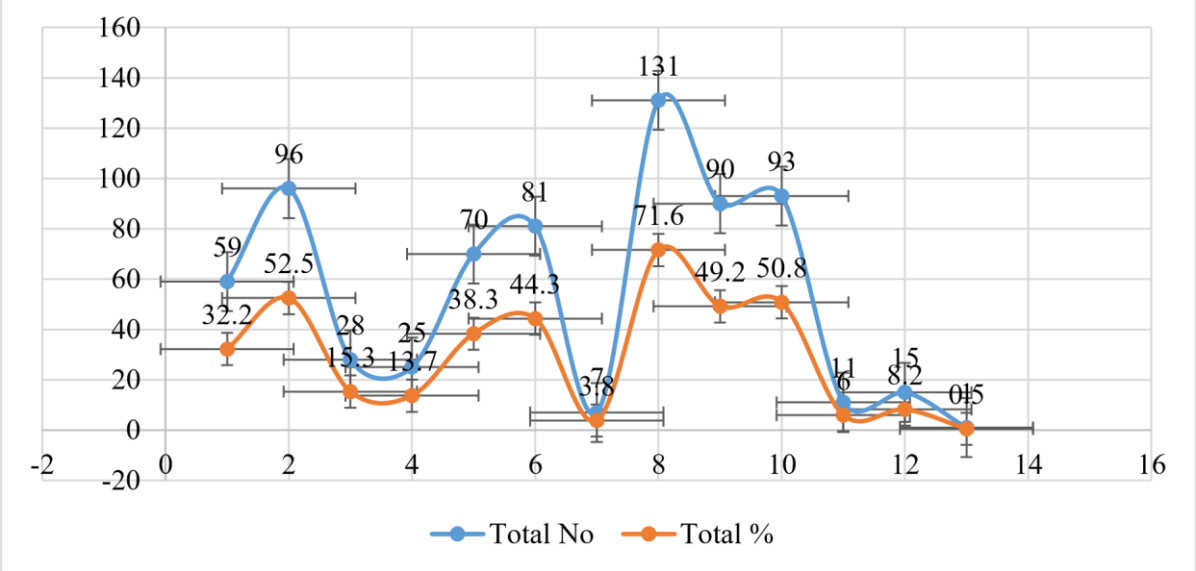


Table – II: Characteristics among outcome of PoUL (183)

Variables		ECTOPIC		F_PUL		IUP		P_PUL		Total	
		No	%	No	%	No	%	No	%	No	%
Age Bracket	17-25 Years	4	2.2	35	19.1	18	9.8	2	1.1	59	32.2
	26-35 Years	8	4.4	47	25.7	35	19.1	6	3.3	96	52.5
	36-46 Years	2	1.1	18	9.8	5	2.7	3	1.6	28	15.3
Gestational Age	4 Weeks	1	0.5	7	3.8	15	8.2	2	1.1	25	13.7
	5 Weeks	2	1.1	43	23.5	24	23.1	1	0.5	70	38.3
	6 Weeks	10	5.5	45	24.6	19	10.4	7	3.8	81	44.3
	7 Weeks	1	0.5	5	2.7	0	0	1	0.5	7	3.8
Symptoms	Amenorrhea	12	6.6	83	45.4	30	16.4	6	3.3	131	71.6
	Bleeding	10	5.5	62	33.9	11	6	7	3.8	90	49.2
	Pain	5	2.7	46	25.1	36	19.7	6	3.3	93	50.8
	Previous Ectopic	2	1.1	8	4.4	0	0	1	0.5	11	6
Methotrexate	1 Injection	4	2.2	0	0	0	0	11	6	15	8.2
	3 Injections	1	0.5	0	0	0	0	0	0	1	0.5



DISCUSSION:

The collection of hCG value and symptoms for the evaluation of a woman with symptomatic 1st trimester pregnancy. The history of uterus TVs and adnexa is also required if indicated. We can observe women with PoUL at their 1st presentation as serial β-hCG and TVS until an accurate diagnosis. Women with PoUL having no or minimal symptoms are prone to the risk of having EP, thus require EM with (48-72) hours follow-up. Accurate clinical prediction of PoUL outcome can shorten a patient's duration of reaching an exact diagnosis. Patients with risk of having EP require accurate and in-time diagnosis because delay can lead to risks of mortality and morbidity. However, intervening early can lead to harming an early IUP. There must be a balance between EP risks with its complications and frequent tests as these tests can deceive with false-positive outcomes [11]. Keeping in

view clinical determination and risk factors, a patient's personal assessment may help in mortality and morbidity reduction. In our study, we managed some patients as 'out-patients' relative to their EP history, symptoms, compliance for follow-up, and β-hCG level. We called these patients for β-hCG and TVS twice and once a week respectively to observe PoUL outcome. Women with EP visualized initially on TVs have higher rupture risks than women with EP presented with PoUL. The common-most outcome (44%-69%) of PoUL is failing PoUL [12-17]. We observed 54.60% comparable results of failing PoUL in our study. Because of small size, early IUP is not clearly visible leading to PoUL diagnosis [3, 18]. Various studies show (30%-37%) patients with IUP post-diagnosis of PoUL [3]. We found comparable outcome (31.70%) for IUP after PoUL diagnosed initially. Various studies reported (8.10%-42%) cases of PoUL ending up at EP outcome. When EP is visualisation-based of adnexal mass instead of intrauterine sac absence on TVS, SSUs (Specialised Screening Units) are used to observe lower (8%14%) values [13, 19 – 20]. The rate of persistent PoUL is 2% of all PoUL [21]. Our study found this rate as 6% perhaps due to MM after 03 β-hCG plateau values. Our early intervention was due to low literacy and poor compliance in our population. More wait on our part could lead to persistent PoUL resolving as failing PoUL or converting to EP. The available data of MM of PoUL is limited. A study reported the successful use of methotrexate (50 mg/m^2) among women with serum-β-hCG level resolution subsequently [9, 10]. The effectiveness of methotrexate is reported as 90% effective in MM [3]. In our study, among 5 and 11 patients having EP and persistent PoUL respectively were resolved with methotrexate single injection with 100% outcome (except one EP patient needing 3 injections). As per hospital protocol, we treated 03 plateau β-hCG values patients medically. Our study did no choose diagnostic methods like tumour markers, serum-progesterone, and mathematical models. According to reports, these methods increase diagnosis with outcome prediction of PoUL. However, validation requires further studies. This research is easy-to-carry-out in most of the average health-care centres.

CONCLUSIONS:

TVS and serial β-hCG levels are important in the determination of the outcome of PoUL. Determining EP early is important to avoid maternal morbidity and mortality. EM is the choice of management for asymptomatic patients with PoUL. EM of patients suspected with PoUL either resolve into IUP or failing PoUL. Most of the EP and persistent PoUL can undergo MM. Few patients with EP may require SM.

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