

# Combined use of cell phone technology, serum Progesterone and $\beta$ -HCG can reduce the extra visits in the management of pregnancy of unknown location in law resource settings

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## ABSTRACT

**Objectives:** The aim of this study was to evaluate efficacy and safety of the combined use of mobile phone and serum progesterone in the management of patients with pregnancy of unknown location.

**Material & methods:** A prospective interventional study was introduced to the emergency ward for managing all patients attended to emergency gynecological ward in El Minya maternity university hospital between the period of 1st of August 2010 and 31st of October 2011 whereby clinically stable patients with PUL and serum progesterone level less than 10 nmol/l were discharged after initial visit. Patients were advised to contact emergency mobile number to two dedicated persons (author & co-author) who follow a chart of symptoms & reading of serum levels of progesterone and incorporate the human chorionic gonadotropin ( $\beta$ -hCG) /48 h ratio if necessary. Surgical or medical intervention was offered to all women with persistent or worsening symptoms and non-declining serum  $\beta$ -hCG.

**Results:** During 15 months of the study period (from the 1st of August 2010 and 31st of October 2011), 675 pregnant women had a clinical and ultrasound diagnosis of PUL with serum progesterone level less than 10 nmol/l were attended to our emergency unit. 590 were included in the final data analysis. The final outcomes were four groups, the first one was the normal intrauterine pregnancy group which was diagnosed in 9 (1.5 %) cases. The second group in which 30 (5.1 %) of the recruited cases, had the diagnosis of miscarriage. In the third group, the site of pregnancy was never determined in 538 (91.2 %) cases (neither intra-uterine nor extra-uterine) and they resolved spontaneously without any intervention. The fourth group which was consisted of 13 cases (2.2%) diagnosed as ectopic pregnancy. From the above figures it is well evident that, the initial level of progesterone was found to predict the outcome of PUL. There was significant reduction in the number of visits ( $P < 0.001$ ).

**Conclusions:** The introduced protocol based upon combined use of mobile phone technology, serum progesterone less than 10 nmol/l at low risk of developing complications and if combined with  $\beta$ -hCG 48 h/48 h ratio notification will be effective in reducing the extra visits & costs and help in triaging women with PULs without significant maternity harm especially in law resource settings.

**Keywords:** Pregnancy of unknown location,  $\beta$ -hCG, serum progesterone, Law resource settings.

## INTRODUCTION

The pregnancy of unknown location (PUL) is a term used to describe a situation where there is a positive pregnancy test but no sign(s) of either intra- or extra uterine pregnancy or even evidences of retained products of conception on transvaginal ultrasound [1]. The prevalence of PUL depends on the sonographer's experience as well as the quality of the machine used. Although, the sensitivity of modern ultrasound equipment is very high [2], but still in many cases the location of pregnancy cannot be determined on initial scan. The diagnosis of PUL leads to urgent clinical assessment and estimation of serum beta human chorionic gonadotrophin ( $\beta$ -hCG) where a number of different protocols have been recently used in order to differentiate between viable intrauterine pregnancies and pathological ones in PUL patients using serial measurements of serum  $\beta$ -hCG [3]. The combined use of ultrasound and serum  $\beta$ -hCG using the discriminatory zone has been used extensively [4] with a sensitivity 100% [5] in diagnosing ectopic pregnancy and a positive predictive value 18.2% [6].

Recently, a useful tool in the management of PUL is the assessment of serum proges-

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terone [7]. Elevated serum progesterone levels indicating the viability of the corpus luteum while its decrease indicating failing of the pregnancy. in a meta-analysis study done by Mol BW et al has Shown serum progesterone levels <25 nmol/l to be associated with nonviable pregnancy, although viable pregnancies (0.3%) have been reported with initial levels <15.9 nmol/l [8]. The same study showed that Levels >25 nmol/l is likely to indicate intrauterine pregnancy while levels >60 nmol/l are strongly associated with pregnancies subsequently shown to be intrauterine, although a small proportion of ectopic pregnancies (2.6%) have been reported with a serum progesterone concentration of >60 nmol/l. If the diagnosis of PUL is established in asymptomatic patient, the guidelines of early pregnancy association recommends conservative management in the form of estimation of serum  $\beta$ -hCG at 48 Hours to detect the pattern of the hormone and follow up accordingly [9].

As it was demonstrated from previous many studies [10], the fast majority of PUL is low risk and a small proportion being ectopic in which 15% will be resolved spontaneously. So, there is emerging consensus to offer the expectant management protocol to all clinically stable patients [11]. This should help to avoid unnecessary operative interventions, but this is on the expense of multiple visits to an early pregnancy assessment unit before a diagnosis can be made. The reported number of visits is 3 visits (with range from 2-6) within 5 days (with range from 2-25).

Nowadays, Mobile phones used widely by staff in different issues concerning patients. Interference with medical equipment inside hospitals appears to be not a serious problem as users are keen to not use cell phones near the equipment [12]. It plays a really important role in the developing countries in different aspects of medicine. It is much easier to reach doctors in case of an emergency. Also we all have cell phones and there is a wide range of area for mobile phone coverage. At a more complex level, mobile phones are being used to improve and increase compliance with taking medications.

The prevalence of PUL varies from 7-31% in women attending early pregnancy units [13] & [14], so it does represent a major burden to the health service facilities despite its benign course. It is therefore essential to develop protocols to reduce the number of extra-visits and subsequently the extra-costs without of course endangering the safety of the women.

A single visit strategy [15] proposed to reduce the number of visits was shown to be unsafe as 67% of women with ectopic pregnancy were discharged without adequate follow-up. Introducing a protocol to reduce these extra visits in such low risk cases appears to reduce the burden to the health service providers as well as on the patients.

The aim of this study was to assess the use of cell phone technology between the clinicians and the patients to triage women with PUL through assessment of symptoms and serum levels of  $\beta$ -hCG and progesterone that could reduce the extra visits in low resource settings.

## MATERIAL & METHODS

A prospective interventional study was introduced to the emergency ward for managing all patients attended to emergency ward in El Minya maternity university hospital between the period of 1st of August 2010 and 31st of October 2011 whereby All clinically stable patients with the diagnosis of PUL (positive serum pregnancy test, no detected either intrauterine or extra uterine pregnancy by transvaginal ultrasound with no evidence of retained products of conception) and serum progesterone level less than 10 nmol/l were discharged after initial visit. All cases were invited to the research project after full explanation of the idea of the project, possibility to withdraw without prior notice without affection of her care. A written consent in Arabic language was taken from each participant with 3 copies (one for authors, the second will be kept in the hospital file and the third one for the participant). In all cases a full medical history is taken and clinical assessment is performed by the clinician in charge. All demographic, clinical, ultrasound and laboratory findings are recorded in a clinical file. The main collected data are the women's age, menstrual history, past obstetric history, transvaginal findings (endometrial thickness, any adnexal findings), serum  $\beta$ -hCG and progesterone measurements. Exclusion criteria were: an early pregnancy sac-like structure within the uterine cavity that required ultrasound follow-up for confirmation of viability, an adnexal mass suspicious of ectopic pregnancy, clinically unstable women, indirect signs of a specific pregnancy location (e.g. hemoperitoneum) and the presence of products of conception that could be visualized either by transvaginal ultrasound or on speculum examination.

Patients were advised to contact emergency mobile number(s) to one of the two dedicated persons (author & co-author) who follow a agreed chart (Figure 1) of symptoms & reading of serum levels of progesterone and incorporate the human chorionic gonadotropin ( $\beta$ -hCG) /48 h ratio if necessary. The group of participants who were free of symptoms (pain & bleeding) with declining of both serum  $\beta$ -hCG (below 25 IU/L) & progesterone offered no further visits. The group who developed worsening of symptoms are advised to attend to the emergency ward immediately irrespective of the serum readings. When the location of pregnancy had been determined on the follow-up scan, the women were managed according to the protocol described below. Surgical or medical intervention was offered to all women with persistent or worsening symptoms and /or abnormal levels of serum  $\beta$ -hCG.

The final outcomes were normal intrauterine pregnancy, miscarriage, ectopic pregnancy, failing pregnancy (whether intra or extra uterine) and persistent PUL. Spontaneously resolving pregnancies are applied to all abnormal pregnancies that did not require any form of intervention (medical or surgical). They included all failing pregnancies as well as all miscarriages and ectopic that were eventually detected on ultrasound scan during follow-up, but then resolved spontaneously on expectant management.

Normal pregnancy was diagnosed by the presence of a live embryo with an intrauterine gestational sac on follow-up scans, while early embryonic demise was diagnosed in women with an empty intrauterine gestational sac >25 mm or a sac with an embryonic pole with crown-rump length >10 mm with no visible heart action on follow-up scans [16]. Miscarriage was diagnosed if there was no evidence of progressive pregnancy growth on two scans at least 2 weeks apart or measurements below the mentioned figures. Incomplete miscarriage was diagnosed in women with evidence of well-defined hyperechoic tissue within the uterine cavity with typical ultrasound features of retained trophoblastic tissue. An

ectopic pregnancy was diagnosed when a pelvic swelling with morphological features typical of an ectopic pregnancy was eventually detected on follow-up scans.

All statistical analyses were carried out using SPSS version 16 (SPSS, Chicago, IL, USA). The outcomes were dichotomized into intervention and no intervention categories. Comparison of the means of continuous variables was performed using the Mann-Whitney U-test or Student's t-test depending on data distribution. Proportions were compared using Yates corrected Chi-square test, and  $P < 0.05$  was considered statistically significant.

## RESULTS

During 15 months of the study period (from the 1st of August 2010 and 31st of October 2011), 675 pregnant women had a clinical and ultrasound diagnosis of PUL with serum progesterone level less than 10 nmol/l were attended to our emergency ward in El Minya university maternity hospital which is a tertiary centre located at the upper Egypt serving about 5 million population. Follow-up was incomplete in 65 cases due to failure to contact them in the follow-up period by the given contact details (phone numbers & home address). 20 cases preferred to go for private care outside the university hospital and they withdrawn from the study after being consented. The remaining 590 were included in the final data analysis.

The final outcomes were four groups, the first one was the normal intrauterine pregnancy group which was diagnosed in 9 (1.5 %) cases on follow-up scan after doubling ratio of the  $\beta$ -hCG titer and serum progesterone level more than 60 nmol/l. They offered the 2nd visit after raising of the  $\beta$ -hCG titer more than 1500 unit where definite viable intrauterine pregnancy was confirmed. In this group no extra visits were needed and they continued their usual antenatal care as planned. The second group in which 30 (5.1 %) of the recruited cases, had the diagnosis of miscarriage. In the third group, the site of pregnancy was never determined in 538 (91.2 %) cases (neither intra-uterine nor extra-uterine) and they resolved spontaneously without any intervention. In this group the mean number of visits was  $3 \pm 1$  till  $\beta$ -hCG titer below 25 unit. The fourth group which was consisted of 13 cases (2.2%) diagnosed as ectopic pregnancy.

The second group (those who had miscarriage), 9 cases (1.5%) required intervention (surgical evacuation of retained products of conception due to persistent clinical symptoms and/or medical therapy by using PGs), and the remaining 21 (3.6 %) women were managed expectantly until the products of conception were spontaneously expelled from the uterine cavity.

In the group in which the final diagnosis was ectopic, five cases (0.8 %) had intervention (three cases of them had surgical intervention e.g. salpingosotomy & salpingectomy and two cases managed by methotrexate). Eight cases managed conservatively. This group showed suboptimal rise or decline of the  $\beta$ -hCG titer by cell phone follow-up and progesterone level between 10-20 less nmol/l. The mean visits were  $3 \pm 1$ . They asked to attend for extra unusual visits for the worsening pain or continues spotting. From the above figures it is well evident that, the initial level of progesterone was found to predict the outcome of PUL.

The overall intervention rate in our study group was 2.3 % (14 cases) cases. Comparing the 2 groups (who had intervention and who had not) showed significant differences in maternal age, gestational age, history of previous abnormal early pregnancy and initial serum  $\beta$ -hCG levels among women who did and did not require medical intervention (Table 1).

## DISCUSSION

The majority of PUL is of low risk and it does represent a major burden on the resource settings. Many authors accept the philosophy of reducing interventions in patients with PUL but this of course must not be at the expense of maternity safety. Having Saied that, the use of modern technology e.g. cell phone by expert clinician and the use of prepared flow chart of symptoms to diagnosis the possible fates of PUL and combined results of serum  $\beta$ -hCG and progesterone may reduce the need to do extra visits and consequently reduce the burden to the health service without endangering the maternity safety.

In our study, normal intrauterine pregnancy group was diagnosed in 9 (1.5 %) cases on follow-up scan after doubling ratio of the  $\beta$ -hCG titer and serum progesterone level more than 60 nmol/l. cases which is similar to study done by Day et. Al [17]. However, this figure is lower than that mentioned in several studies [18] & [15], and this can be explained by the using cut off level of serum progesterone less than 10 nmol/l in our series. They were offered the 2nd visit after raising of the  $\beta$ -hCG titer more than 1500 unit where definite living intrauterine pregnancy was confirmed. In this group no extra visits were needed and they continued their usual antenatal care as planned, so the mean number of visits was one.

The second group in our study, 30 (5.1 %) of the recruited cases, had the diagnosis of miscarriage by ultrasound and, the  $\beta$ -hCG titer neither failed to raise optimally or decline sub optimally and those patients were attended for additional visit after heavy bleeding of severe pain or invited for visit if no further complaint to diagnose missed miscarriage. In such group, 9 cases (1.5%) required intervention (surgical evacuation of retained products of conception due to persistent clinical symptoms, and medical therapy by using PGs), and the remaining 21 (3.6 %) women were managed expectantly until the products of conception were spontaneously expelled from the uterine cavity. The mean number of visits in this group was  $2 \pm 1$ . Some patients from this group attended to the emergency unit with severe bleeding and/or pain and offered surgical evacuation of the uterus after settling the diagnosis of miscarriage.

The third group, the site of pregnancy was never determined in 538 (91.2 %) cases (neither intra-uterine nor extra-uterine) and they resolved spontaneously without any intervention. In this group the mean number of visits was  $3 \pm 1$  till  $\beta$ -hCG titer below 25 unit and serum progesterone never raised above 10 nmol/l. This category represent the major score in our study and showed difficulty to be counseled by the authors about the fate of their pregnancy. They were advised to attend for re-evaluation & reassurance if they worried. This could explain the higher number of visits in such group rather than the need for further assessment.

Identification of this group and proper diagnosis is essential step for counseling for further pregnancies. While the diagnosis of failed ectopic necessities the future counseling about the possibility of future recurrence, the diagnosis of failed intra-uterine pregnancy necessities the investigation of recurrent early pregnancy loss.

The fourth group which was consisted of 13 cases (2.2%) diagnosed as ectopic pregnancy. In this group, five cases (0.8 %) had intervention (three cases of them had surgical intervention e.g. salpingosotomy & salpingectomy and two cases managed by methotrexate) and eight cases managed conservatively. The intervention rate in this group was comparable to previous studies [10], [11], [3], [19] & [15]. Our intervention rate reflect our recent tendency to manage the stable and asymptomatic ectopic cases



conservatively and this is our target. also in this group we had 2 cases of ruptured ectopic came to us with picture of mild pelvic collection and were subjected to laparoscopic intervention in the form of salpingectomies. The patients who had ruptured ectopic were advised to attend to the emergency ward as they have severe pain with suboptimal rise of serum  $\beta$ -hCG and progesterone level between 10-20 u/ml. In this issue we need to ensure the safety of conservative management for all women so they have to be educated about the symptoms of intra-abdominal bleeding and they should be provided with immediate access to emergency facilities in case of worsening clinical symptoms. In the ectopic group, we had two cases presented with a history of heavy vaginal bleeding and are found to have suboptimal decline of  $\beta$ -hCG and serum progesterone less than 10 nmol/L with picture of trans-vaginal ultrasound showed empty uterus with no adnexial suspicious of ectopic. Decision to admit those cases was taken as the consultants in charge did not assumed to have had complete miscarriage but rather classified as PUL. Follow-up of the two cases showed picture suggestive of ectopic. One case of them managed conservatively while the other managed by methotrexate.

In a previous study done prospectively to diagnose IUPs and ectopic pregnancies on the basis of three visits within 7 days and failing PULs on the basis of two visits within 2 days. The results showed that 97.5% of women with PULs were given a diagnosis (IUP, failing PUL or ectopic pregnancy) by day 7 and 88.7% of these were confirmed using the planned number of visits [20]

Our main objective of combining the triple use of cell phone technology, serum  $\beta$ -hCG and progesterone level is to assess the intervention rate in each individual case and to calculate the mean visits required until reaching the final diagnosis and managing the case and so limiting wasting of resources especially in our countries and so focusing these available resources to the high risk cases. Extra benefits of reducing the visits will be reflected on the social and economical burden of the families who pay the whole cost of health service in low resources settings. On the other hand, repeated visits is associated with poor compliance and disruption of the life in working women. In our study, Follow-up was incomplete in 65 cases due to failure to contact them in the follow-up period by the given contact details (phone numbers & home address) and 20 cases preferred to go for private care outside the university hospital and they withdrawn from the study after being consented. The explanation of this high numbers could be due to non preferring the general sector of health care and preferring the private one which is costing too much and carries a big burden to the economic state of the families. Another explanation is the huge number of attendants to the hospital daily which could be reflected on the service quality as explained by some attendants. The high non-compliance rates which was similar in a study done by Kirk [3] is alarming as this may lead to delayed diagnosis of high risk cases with subsequent morbidities and may mortalities even. So, reducing the number of extra visits could save resources of both the (patients & country), and more importantly divert the efforts of the health professionals to the high risk case to avoid complications provided that probably selected criteria for high and low risk subgroups. The strategy of single visit in managing low risk patients with PUL has already been discussed in many previous publications.

In our study, when we combining serum progesterone level  $\leq 10$  nmol/L and the doubling ration of serum  $\beta$ -hCG notified by cell phone to dedicated expert personnel complying to a flow chart of symptoms can reduce the extra visits in low risk group without endangering the maternity safety and reassure the client if there is no other warning symptoms and this noticed to be associated with very low risk cases. However, this combination cannot complete-

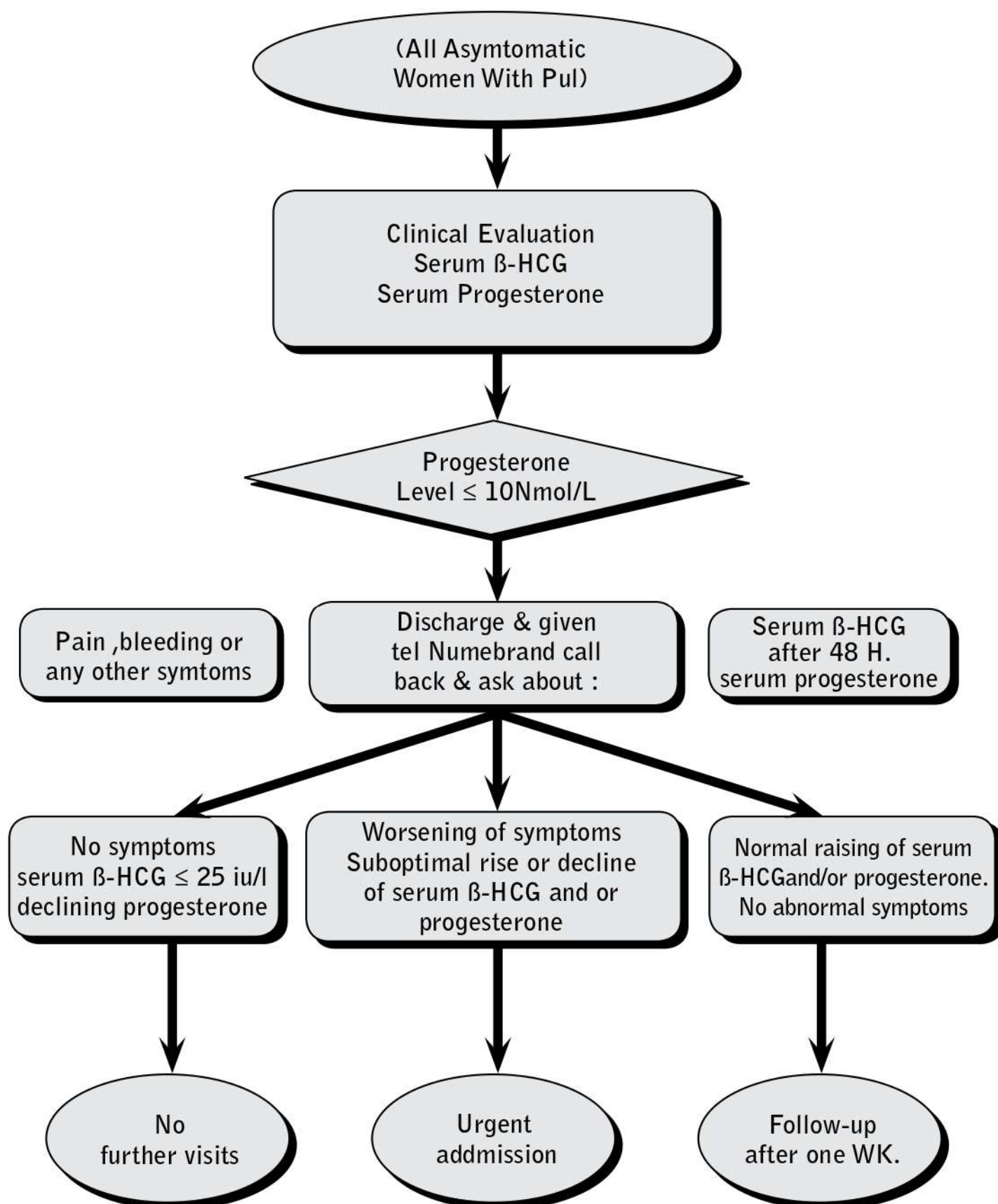
ly eliminate the need for follow-up visits especially in women with abnormal serum readings or complained symptoms.

The rate of subsequent intervention rate in this group was found to less than 3% in ectopic or miscarriage cases. So, it is well evident from our results that such combination strategy (flow chart symptoms, serum  $\beta$ -hCG & serum progesterone level  $\leq 10$  nmol/L) can eliminate more than 50% of unnecessary visits without significant increase in the adverse outcomes.

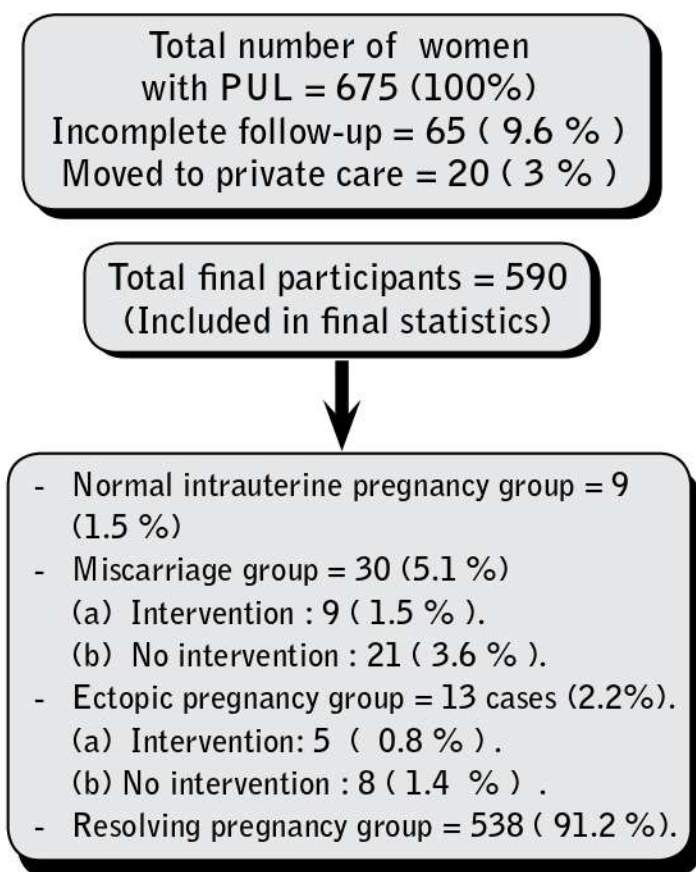
The cornerstone advice from this study is to select the proper patient to be subjected to such new protocol and in case of worries from either the patient, family or the treating doctor, admission to the inpatient sector under monitoring should be the best option to have.

In conclusion, initial clinical evaluation and serum progesterone level  $\leq 10$  nmol/L, with proper serum  $\beta$ -hCG interpretation, and the use of cell phone technology can reduce the extra visits and hereby reduce the extra costs and may divert the efforts towards more risky cases without endangering the maternity life. Of course, this combination needs to be evaluated prospectively in a large study in order to assess its efficacy and safety and before all the community acceptability, cost-effectiveness and its complications if any.

Figure (1): Flow chart of the study:





**Figure (2):****Table (1):**

Comparison of demographic, clinical and biochemical findings in women with pregnancies of PUL at the initial visit in respect to the need for intervention.

	Intervention group (14)	Non – interventional group (576)	Significance (P value)
Maternal age	33.6 ± 5.6	28.9 ± 4.6	0.010
Gestational age (days)	43 ± 10.4	48 ± 9.4	0.003
Previous abnormal pregnancy	110	210	0.010
Initial serum B-hcg IU/L	812 ± 410	324 ± 214	0.002

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