Pregnancy of unknown location as a diagnostic challenge – case analysis

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SUMMARY

Introduction: Pregnancy of unknown localization (PUL) is a diagnostic challenge within the population of the patients with increased serum b-hCG as well as no ultrasonographic confirmation of an intrauterine nor extrauterine pregnancy. Creating a universal approach and diagnostic method regarding this matter could help us reduce the risk of serious complications such as life-threatening events following the development of an extrauterine pregnancy.
Aim of the study: The aim of this study was to determine the distribution of the final diagnoses and their basic characteristics among the population of the patients admitted with the initial diagnosis of PUL to the II Dept. of Obstetrics and Gynaecology Wroclaw Medical University.
Material and methods: We analysed 44 patients' histories who were hospitalised between 2016-2017 within the 2nd Dept. of Obstetrics and Gynaecology Wroclaw Medical University with an initial diagnosis of PUL. Collected data was then analysed using STATISTICA software.
Results: The mean age of patients was 31y.o., mean number of pregnancies 1.9, mean pregnancy length was 6 weeks. 36 women (81,6%) were admitted presenting clinical symptoms, 8 cases (18,2%) were asymptomatic.
Conclusions: Ectopic pregnancy was the most common end-diagnosis in the tested group. The frequency of ectopic pregnancy, miscarriage and PUL as the end-diagnosis increases with the patient's age.
Key words: pregnancy; location; ultrasound examination; PUL

INTRODUCTION

A pregnancy of unknown location (PUL) is defined as a pregnancy confirmed in laboratory tests in which the location of the fertilized egg cannot be determined in ultrasonography [1,2]. PUL itself is not a diagnosis, but a description of a clinical situation that requires further and thorough diagnosis, particularly in women presenting with clinical signs, such as uterine bleeding, abdominal pain or episodes of syncope [1–3]. The incidence of PUL in pregnant patients hospitalized at early pregnancy pathology departments ranges from 8–31% according to the literature [1,4]. The authors generally assume that this percentage will decrease with improved imaging quality and sensitivity. In the diagnostic process of early pregnancy, patients can be classified into one of four categories: normal intrauterine pregnancy (IUP), spontaneous miscarriage (failed PUL), ectopic pregnancy (EP) and pregnancy of unknown location [1,2,5]. The International Society of Ultrasound in Obstetrics and Gynecology intends to lower the frequency of PUL to the level below 15%. A delay in the diagnosis of an ectopic pregnancy may lead to severe complications: increase mortality and emergency surgical interventions. On the other hand, a suspicion of an ectopic pregnancy made too early may result in unnecessary and burdening surgical interventions, especially in cases of normal intrauterine pregnancies [1,3]. These arguments indicate how important it is to develop effective diagnostic algorithms enabling one to establish an initial diagnosis early. There are no clear diagnostic criteria for cases of early intrauterine and ectopic pregnancies [1–3,7]. Most diagnostic schemes are based on ultrasonography, establishing the cut-off levels for chorionic gonadotropin (hCG) at which a pregnancy should be visible in the uterus using a transvaginal transducer and serial chorionic gonadotropin assays with assessment of the relationship between day 0 value and the value obtained after 48 hours [1,2,7].

An intrauterine pregnancy is established on ultrasonography by: the presence of a gestational sac (about 4.5–5 weeks of gestation), yolk sac (about 5 weeks of gestation) and an embryo with visible cardiac activity (about 5.5–6 weeks of gestation). An ectopic pregnancy presents on ultrasonography as: the presence of an irregular structure of mixed echogenicity within the uterine adnexa (60%) with an accompanying intrauterine pseudo-sac (20% of cases), free peritoneal fluid (56%), gestational sac within the adnexa with an embryo either with or without cardiac activity (20%) [2,8]. The chorionic gonadotropin cut-off value at which a pregnancy should be visible is, according to various authors, 1,000–1,500 IU/L. However, it is not commonly used as a diagnostic method due its low diagnostic value [1,5,9]. Serial ß-hCG assays enable one to assess the dynamics of its serum levels and, when supplemented with ultrasonography, allow the verification a pregnancy of unknown location [7,10].

Some therapeutic schemes assume additional diagnostic methods, such as: evaluation of endometrial thickness, margins and volume, assessment of ovarian volume, Doppler examination of flow within the endometrium, ovarian vessels and corpus luteum as well as assessment of the activity of activin A, inhibin A, pro-alpha C-RI inhibin, insulin-like growth factor BP-1 (IGFBP-1) and CA-125 antigen [1,2,11]. These tests are characterized by low specificity and are not commonly included in a diagnostic scheme.

AIM

The aim of the study was to analyze the diagnostic process and ultimate diagnoses in women hospitalized due to a pregnancy of unknown location in 2016–2017 in the Second Clinic of Gynecology and Obstetrics in Wrocław, Poland.

MATERIAL AND METHODS

We analyzed 44 women hospitalized due to a pregnancy of unknown location in 2016-2017 in the Second Clinic of Gynecology and Obstetrics in Wrocław, Poland. The analysis included patients' age, obstetric history, gestational age at admission, chorionic gonadotropin level and ultimate diagnosis at discharge. Moreover, the incidence of symptoms indicating early pregnancy pathology was also assessed. The data obtained were analyzed statistically using the STATISTICA system.

RESULTS

From January 1 2016 to March 20 2017, 44 patients with a pregnancy of unknown location were hospitalized. The mean age of the patients was 31 years, mean parity 1.9 pregnancies and mean gestational age 6 weeks. During hospital stay, a viable intrauterine pregnancy was found in 4 cases, which constituted 9% of all patients. The mean chorionic gonadotropin level was 11,192 IU/L with the mean age of 28.5 years, parity of 1.75 pregnancies and mean gestational age of 6 weeks. Miscarriage was ultimately diagnosed in 16 patients, which constituted 36.4% of cases, with the mean gonadotropin level of 1,271 IU/L, mean age of 31 years, parity of 1.5 pregnancies and mean gestational age of 6.9 weeks. Patients with an ectopic pregnancy (18) constituted 41% of the group. Five of them had a ruptured ectopic pregnancy with bleeding to the peritoneal cavity; their the mean chorionic gonadotropin level was 10,239 IU/L. In the remaining patients with an ectopic pregnancy the chorionic gonadotropin value was 1,422 IU/L. The mean age of patients with an ectopic pregnancy was 33 years, parity was 2.4 pregnancies and gestational age was 6 weeks. The last group included patients who were discharged

Tab. 1. Characteristics of PUL patients depending on the final diagnosis. vIUP – viable intrauterine pregnancy, EP – ectopic pregnancy, pPUL – pregnancy of unknown location – a final diagnosis

	vIUP	Miscarriage	EP	pPUL	Mean for all patients
Age	28,5	31	33	31	31
Parity	1,75	1,5	2,4	1,2	1,8
Gestational age	6	6,9	6	6	6
Mean beta-hCG level [IU/L]	11 192	1271	1422	162	3064
Number of patients with a given diagnosis	4 (9%)	16 (36,4%)	18 (41%)	6 (13,6%)	44 (100%)

with a diagnosis of a pregnancy of unknown location – 6 cases, i.e. 13.6% of the whole group, with the mean chorionic gonadotropin level of 162 IU/L, age of 31 years, parity of 1.2 pregnancies and gestational age of 6 weeks. There were no statistically significant differences for parity and gestational age in the analyzed group. Statistical significance was found for chorionic gonadotropin levels, with the highest values observed in viable intrauterine pregnancies (Tab. 1 and 2).

At admission, 36 patients (81.8%) presented with clinical signs in the form of vaginal bleeding and pelvic pain. Eight patients (18.2%) reported no symptoms.

DISCUSSION

Determination of the gestational sac location is still a considerable challenge despite the progress in early pregnancy diagnosis that has taken place in the recent years. Prompt diagnosis is significant since it enables one to implement adequate treatment and limit severe complications associated with abnormal location of the fertilized egg. Due to the higher risk of serious complications, exclusion of an ectopic pregnancy is a priority in the diagnostic process in PUL patients. In most cases of a pregnancy of unknown location reported in the literature (50–70%), the ultimate diagnosis was a miscarriage [12–14]. The percentage of ectopic pregnancies in the authors' own study was 41% and was the highest. Various authors report that the rate of ectopic pregnancies ranges from 6–20% [13,15]. The results of our study confirm that

if one is unsure about the location of the gestational sac in early pregnancy, an ectopic pregnancy should be considered in the first place.

The literature states that clinical sings in the form of uterine bleeding and/or abdominal pain are reported in 25–30% of all pregnancies, and their occurrence increases the risk of early pregnancy pathology [16]. These clinical signs were also present in most of our patients, which confirms this relationship. Women with a pregnancy of unknown location require particular systematization in terms of the risk of an ectopic pregnancy. An example scheme enabling classification of a given case to a group of decreasing probability of an ectopic pregnancy has been developed [2,3]. The first group encompasses women with a definite ectopic pregnancy on imaging (extrauterine gestational sac with yolk sac, embryo and cardiac activity). The second group includes patients with a probable ectopic pregnancy (a non-homogeneous structure within the adnexa). The third group consists of patients in whom neither intrauterine nor ectopic pregnancy can be confirmed (so-called "true" PUL). The fourth group includes patients with a probable intrauterine pregnancy (a sac-like structure without an embryo echo in the uterus), and the fifth – patients with a definite intrauterine pregnancy on ultrasonography (intrauterine gestational sac with yolk sac and embryo) [1,3]. This division is justified and helpful since it enables the classification of a given patient to a clinical class, preliminary estimation of the risk of possible complications and decisions about further diagnostic and

Tab. 2. Age of PUL patients and mean beta-hCG values in a classification according to the final diagnosis. vIUP – viable intrauterine pregnancy; mIUP – miscarried intrauterine pregnancy; EP – ectopic pregnancy; PUL – pregnancy of unknown location

Final diagnosis	Mean age (years)	Beta – hCG (IU/L)
vIUP	28,5	11 192
mIUP	31	1271
EP	33	1 422
PUL	31	162

Tab. 3. Initial and final diagnoses in patients with PUL. definite EP – definite ectopic pregnancy; probable EP – probable ectopic pregnancy; PUL – pregnancy of unknown location; probable IUP – probable intrauterine pregnancy; definite IUP – definite intrauterine pregnancy. vIUP – viable intrauterine pregnancy; mIUP – miscarried intrauterine pregnancy

	Initial diagnosis	Final diagnosis
Definite EP	**1** (2,3%)	**18** (41%) - EP
Probable EP	**12** (27,3%)	
PUL	**22** (50%)	**6** (13,6%) - PUL
Probable IUP	**8** (18,2%)	**20** (45,5%) -
Definite IUP	**1** (2,3%)	**4** (9%) vIUP + **16** (36,4%) mIUP

therapeutic process. In a retrospective analysis, the risk groups were specified for the patients hospitalized due to PUL based on an initial ultrasound scan. Of 4 patients with a viable intrauterine pregnancy detected during the hospital stay, 3 cases were classified to the group of a probable intrauterine pregnancy and 1 to the definite intrauterine pregnancy group. Of 16 patients with miscarriage, 5 were classified as probable intrauterine pregnancy, 10 as "true" PUL and 1 as probable ectopic pregnancy. In 18 patients with an ectopic pregnancy, one patient with ruptured fallopian tube was classified as definite ectopic pregnancy, 12 cases as probable ectopic pregnancy and 5 cases were placed in the third group ("true" PUL). Finally, all 6 patients with an ultimate diagnosis of a pregnancy of unknown location were initially classified to the "true" PUL group. The collective results of this retrospective analysis are shown in Table 3.

The current management standard in cases of a suspected ectopic pregnancy assumes serial ß-HCG assays and a transvaginal ultrasound scan [6,7,10,17–21]. Unfortunately, ultrasonography is of limited value in over 27% of early pregnancies [8] since, by contrast with ß-HCG, a longer time is needed for an increase in the size of a gestational sac to enable its visualization. Difficulties in visualizing early pregnancy on ultrasonography and high frequency, up to 31%, of pregnancy of unknown location result in the fact that this modality gains value with the progression of pregnancy [1,4]. In our opinion, laboratory ß-HCG assays are more significant in very early pregnancies (up to week 4.5–5) with concomitant clinical symptoms, which is confirmed in other reports [2,8].

In our study, the mean chorionic gonadotropin value at admission was 3,064 IU/L. It differs from the mean value reported by Kirk et al., which was lower and equaled 635 IU/L (8). The mean age of patients with a pregnancy of unknown location was 31 years, and the mean duration of pregnancy was 6 weeks. These findings are similar to Kirk et al. where the respective values were 32 years and 6 weeks (8). In our material, the highest ß-HCG levels were found in patients with a viable intrauterine pregnancy. They exceeded the values noted in the ectopic pregnancy group significantly (11,193 IU/L and 1,422 IU/L, respectively). Similar marked differences between ß-HCG levels for intrauterine and ectopic pregnancies have been reported by other authors. According to Reid et al., the value for an intrauterine pregnancy was three times higher than the value for an ectopic pregnancy, with mean values of 621 IU/L and 190 IU/L, respectively [22]. The levels reported by these authors were lower than ours. There is an age-related increase in the frequency of an ectopic pregnancy (32 years), miscarriage (31 years) and pregnancy of unknown location as a final diagnosis (31 years) compared with normal intrauterine pregnancy (28.5 years). Similar outcomes are reported by others [22].

CONCLUSIONS

The most common final diagnosis in patients with a pregnancy of unknown location is an ectopic pregnancy. The frequency of an ectopic pregnancy, miscarriage and PUL as final diagnoses in patients with PUL increases with the patients' age. It is necessary to carry on the search for effective diagnostic schemes in order to establish the final diagnosis in PUL patients as promptly as possible.

REFERENCES

1. **Amer N, Amer M, Koikaila MA.** Pregnancy of unknown location: Outcome in a tertiary care hospital. *J Pak Med Assoc*. 2015;65(10):1097-101.
2. **Boyraz G, Bozdag G.** Pregnancy of unknown location. *J Turk Ger Gynecol Assoc*. 2013;1,14(2):104-8. doi: 10.5152/jtgga.2013.74317. ECollection 2013.
3. **Kirk E, Bottomley C, Bourne C.** Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. *Hum Reprod Update* 2014;20:250-261.
4. **Tierney JP, Welsh J, Owen P.** Effective Gynaecology in Glasgow Group. Management of early pregnancy loss—a complete audit cycle. *J Obstet Gynecol* 2006;26(3):229-32.
5. **Sagili H, Mohamed K.** Pregnancy of unknown location: an evidence]based approach to management. The Obstetrician & Gynaecologist 2008 - Wiley Online Library.
6. **Romero R, Kadar N, Jeanty P, Copel JA.** Diagnosis of ectopic pregnancy: value of the discriminatory human chorionic gonadotropin zone. *Obstet Gynecol* 1985; 66(3): 357-60.
7. **Kirk E, Bottomley C, Bourne T.** Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. *Hum Reprod Update* 2014; 20(2):250-61. doi: 10.1093/humupd/dmt047. Epub 2013 Oct 6.
8. **Kirk E, Daemen A, Papageorghiou AT.** Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination? *Acta Obstet Gynecol Scand* 2008;87(11):1150-4. doi: 10.1080/00016340802443822.
9. **Barnhart KT, Simhan H, Kamelle SA.** Diagnostic accuracy of ultrasound above and below the beta-hCG discriminatory zone. *Obstet Gynecol* 1999;94(4):583-7.
10. **Silva C, Sammel MD, Zhou L.** Human chorionic gonadotropin profile for women with ectopic pregnancy. *Obstet Gynecol* 2006;107:605-610.
11. **Condous G, Reid S.** The role of 3D ultrasound in the management of pregnancies of unknown location 2011.
12. **Kirk E, Bourne T.** Pregnancy of unknown location. *Obst, Gynaecol and Reprod Med* 2008;19:3 80-83.

13. **Banerjee S, Aslam N, Zosmer N et al.** The expectant management of women with pregnancies of unknown location. *Ultrasound Obstet Gynecol* 1999;14:231-236.
14. **Condous G, Lu C, Huffel SV et al.** Human chorionic gonadotrophin and progesterone levels in pregnancies of unknown location. *Int J Gynaecol Obstet* 2004; 86:351-7.
15. **Condous G, Kirk E, Lu C et al.** Diagnostic accuracy of varying disriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2005;26:770-5.
16. **Hasan R, Baird DD, Herring AH et al.** Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. *Ann Epidemiol* 2010;20:524–31.
17. **Barnhart KT.** Clinical practice. Ectopic pregnancy. *N Engl J Med.* 2009;361:379–87.
18. **Barnhart K, Mennuti MT, Benjamin I et al.** Prompt diagnosis of ectopic pregnancy in an emergency department setting. *Obstet Gynecol* 1994;84:1010–5. [PubMed]
19. **Nyberg DA, Filly RA, Mahony BS et al.** Early gestation: correlation of HCG levels and sonographic identification. AJR *Am J Roentgenol* 1985;144:951–4. [PubMed]
20. **Kadar N, DeVore G, Romero R.** Discriminatory hCG zone: its use in the sonographic evaluation for ectopic pregnancy. *Obstet Gynecol* 1981;58:156–61. [PubMed]
21. **Peisner DB, Timor-Tritsch IE.** The discriminatory zone of beta-hCG for vaginal probes. *J Clin Ultrasound* 1990; 18:280–5. [PubMed]
22. **Reid S, Nadim B, Bignardi T.** Association between three-dimensional transvaginal sonographic markers and outcome of pregnancy of unknown location: a pilot study.