

CLINICAL STUDY

Sonography in the management of symptomatic pregnancies of unknown location

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Abstract: *Objective:* To evaluate the management of pregnancy of unknown location in our conditions and to assess possibilities to improve on the performance of it.

Methods: This was a retrospective study of a population of women classified as having PUL. Out- and in-patients were recruited. Their medical history, gynaecological examinations, transvaginal sonography and serum β -hCG were carried out. Final outcome of each PUL was established.

Results: Diagnostic models for variant courses of PUL were established. EPs after PUL were evaluated. The following sonographic findings were associated with EP after PUL: blob sign in 4 of 16 cases (25 %), bagel sign in 1 case (6.25 %), EP established by sonography in 2/16 cases (12.5 %) and no valid sonographic structures in 9/16 cases (56.25 %).

Conclusions: Conditions for improvement the management of PUL are: implementation of PUL in the clinical practice, creation of EPU, improvement in the evaluation of serum β -hCG levels and resolution of sonographic examination (Tab. 1, Fig. 1, Ref. 18). Full Text (Free, PDF) www.bmj.sk.

Key words: sonography, management, pregnancy.

The most frequent reason of maternal mortality and morbidity in the first trimester is a rupture of ectopic, extra-uterine pregnancy (EP, ectopic pregnancy). Over the last decades we can see a rise in the occurrence of EP and at present it makes up approximately 2 % of all pregnancies. Early detection and treatment of asymptomatic, non-disrupted EP enables not only to decrease mortality but also ensure next fertility. Moreover, the cost benefit of this approach is considerable too (3).

Spontaneous abortion (SAB) is other pathology of early pregnancy requiring early detection and treatment. It is one of the most frequent complications occurring approximately in 20 % of all pregnancies. Late SAB diagnosis results in treatment delay and in addition the possible complications can have a negative influence on patient's psychological health (15). Delayed treatment and diagnosis in case of threatening abortion can also lead to spontaneous abortion.

However, early detection of pregnancy enables to detect pregnancy that is not prospective or threatens the life or health of patient. Establishing normal intrauterine pregnancy has a positive influence on psychological health of a pregnant woman and it is also important for the management of high-risk pregnancy. In

practice, it often happens that it is not possible to establish whether the pregnancy is intrauterine or extrauterine at the time of initial examination. As this situation can possibly result in above mentioned problems, special attention of clinicians is required here. It is referred to as the pregnancy of unknown location (PUL).

PUL means that a woman has a positive pregnancy test and transvaginal sonography shows an empty uterus with no signs of extrauterine pregnancy (5). In case of asymptomatic PUL it can be a very early pregnancy that is impossible to detect by sonography – or the non-disrupted EP when pregnancy is not visible in the uterus. In case of symptomatic PUL it can be a disrupted EP, or different stages of spontaneous abortion. Therefore, the adequate PUL management is inevitable – i.e. early diagnostics and treatment of pathological stage which can develop in PUL.

Sonography is highly significant in PUL management. Implementation of sonography into the diagnostic algorithm enabled not only early detection of gestational sac but especially its intra- or extra-uterine location. In addition to this, sonography enables to assess adnexal findings, which is inevitable in EP diagnostics, as well as structures of uterus and its surroundings.

Objective of this retrospective study is the assessment of our current sonography possibilities in PUL management, mostly in EP. In the next prospective study we will be following the possibilities of improving this management.

To the best of our knowledge this is the first study on PUL published in Slovak literature.

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Tab. 1. EP in PUL.

No	Ultrasound	β -hCG	Localisation	Operation
1	negat.	880.2; 689.7	tubal	salpingectomy
2	negat.	182.7; 114.7	tubal	salpingectomy
3	negat.	389.7; 517.2; 622; 250	tubal	salpingectomy
4	viable tubal EP	20 260	tubal	salpingectomy
5	negat.	2813; 3137; 3495	tubal	salpingectomy
6	ovarial EP	2336; 1132	ovary	ovarian resection
7	blob sign	3079	tubal	salpingectomy
8	bagel sign	4152;1644	tubal	salpingectomy
9	negat.	107	tubal	salpingectomy
10	blob sign	2118	tubal	salpingectomy
11	blob sign	265; 168.9; 66.3	tubal	salpingectomy
12	negat.	3644; 3849; 6997	cornual	cornual resection
13	negat.	440	tubal	salpingectomy
14	negat.	1450; 557; 623	tubal	salpingectomy
15	blob sign	7609; 8751	tubal	salpingectomy
16	negat.	324.2; 347.1	tubal	salpingectomy

Materials and methods

In the period between 1 January 2007 and 31 October 2007 there were 963 women examined and classified as being in their early pregnancy. Patients were sent to us by their gynaecologists for the establishment of asymptomatic pregnancy or with symptoms of early pregnancy pathology (pain in lower abdomen and/or vaginal bleeding); some of the patients came to us with no recommendation or were driven to us by ambulance.

The initial diagnosis was established on the basis of sonography, gynaecological, or biochemical examination. Ultrasound examination was carried out by transvaginal sonography (TVS). Based on this diagnosis the patients were either sent to out-patient care, or their next visit to our surgery was booked or admitted as in-patients. In former cases (sending patients to out-patient care) normal intrauterine pregnancy was confirmed by sonography. Repeated ultrasound examinations were carried out in women in whom the gestational sac was not shown, i.e. in those with asymptomatic PUL. Hospitalisation was recommended due to three reasons. Firstly, due to the threat of abortion in women with high-risk pregnancy treated by medicaments or upon women's own request. Secondly, due to invasive approach, i.e. surgical intervention – namely D&C in case of spontaneous abortion, LSK diagnosis, or laparotomy in case of EP. Asymptomatic PUL with β -HCG level above the discriminatory zone (i.e. above 1000 IU/l) after having excluded spontaneous abortion was also regarded as EP. Third reason for hospitalisation was the conservative follow-up of patients with symptomatic PUL (pain in lower abdomen and/or vaginal bleeding), namely those diagnosed with Abortus imminens susp., SA susp. and EP susp. In these cases TVS examination and β -hCG measurement were carried out subsequently after 48 hrs until it was possible to establish unambiguously one of the given diagnoses.

We remark that D&C was excluded from the diagnostic algorithm of PUL management. Therefore, we were not using it for diagnosis establishment, but only after establishing PUL. The reason was the fear of unwanted termination of normal pregnancy which is confirmed by the other authors, too (12).

In accordance with other authors (9) we also rejected the single-visit strategy in PUL management due to the fear that EP could be missed.

It is necessary to indicate that in medical records of particular patients, PUL was not stated as a diagnosis as it is only descriptive and not a conventionally used term, and as the particularly used diagnoses were in accord with the Statistical Qualification of Diseases.

We used an ordinary sonographic examination carried out by using Aloka and Esaote systems and TVS with a 5 MHz transvaginal transducer.

Results

A total of 91 patients classified as PUL were recruited – 39 asymptomatic PUL and 52 symptomatic PUL. For simplicity, the retrospective assessment of PUL management in particular cases was carried out according to the final diagnosis.

Asymptomatic PUL included repeatedly followed up out-patients with no clinical problems, whose pregnancy could not be visualised by use of sonography at the time of their initial visit. According to the results of transvaginal sonography examination as well as to the clinical status of the particular patients, the following types of approach were established:

Type A: Repeated ultrasound examination in the period of 2–7 days established normal intrauterine pregnancy. It was not necessary to carry out the measurement of β -hCG. All of them

were cases of pregnancy prior to the fourth week of gestation at the time of their first consultation.

Conclusion: Normal pregnancy

Type B: The repeated ultrasound examination in the period of 2–7 days did not establish normal intrauterine pregnancy. Measurement of β -hCG was carried out. When the level was below discriminatory borderline, patients were again followed up with ultrasound examination. When the level was above this borderline, patients were assigned to hospital under the suspicion of EP.

Conclusion: Persisting PUL

Type C: In period between repeated ultrasound examinations symptoms of early pregnancy pathology occurred. This meant symptomatic PUL and patient was acutely hospitalised. These were cases of disrupted EP as well as cases of spontaneous abortion or threat of abortion.

Conclusion: Symptomatic PUL

Type D: Ultrasound examination directly (with no β -hCG level measurement) detected gestational sac out of the uterus with embryonic pole and/or fetal heart activity present, which was an indication for acute hospitalisation, LSK and salpingectomy.

Conclusion: EP

Symptomatic PUL included patients with clinical symptoms of early pregnancy pathology, i.e. pain in lower abdomen or vaginal bleeding. These were patients with diagnoses of Abortus imminens susp., SA susp. and EP susp. Patients were repeatedly examined with transvaginal sonograph in intervals of 48 hrs and their β -hCG levels were measured. In the management of subsequently diagnosed EP (Tab. 1) some of the following approaches were used:

Type E: The increase in β -hCG level and absence of intrauterine gestational sac at examinations repeated after 48 hrs, unconvincing or suspect adnexal findings (bagel sign or blob sign), LSK and salpingectomy indicated, EP established histologically.

Conclusions: Tubal EP

Type F: The increase in β -hCG level and absence of intrauterine gestational sac at examinations repeated after 48 hrs, adnexal findings negative, suspect findings in other places – in uterine corner, in ovary, LSK and corneal or ovarian resection, indicated EP established histologically.

Conclusions: Extra-tubal EP

Type G: The decrease in β -hCG level, empty uterine cavity, adnexal findings negative, discharge from hospital, subsequent hospitalisation due to the repeated increase in β -hCG level and empty uterine cavity, LSK and salpingectomy indicated, EP established histologically.

Conclusions: EP with temporary decrease in β -hCG level

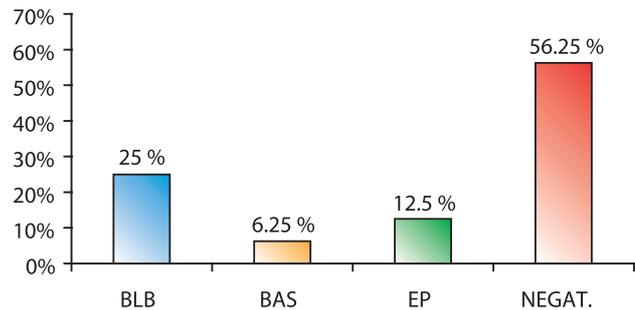


Fig. 1. Sonography examination in PUL with subsequently diagnosed EP showed the following findings. BLB – blob sign, BAS – bagel sign, EP – ectopic pregnancy.

Type H: The decrease in β -hCG level, empty uterine cavity, adnexal findings unconvincing, discharge from hospital, subsequent ambulatory check-up for β -hCG level showed zero values.

Conclusions: EP spontaneously resolved

Sonography examination in PUL with subsequently diagnosed EP showed the following findings (Fig. 1):

Blob sign detected in 4 of 16 cases (25%),

Bagel sign detected once (6.25%),

EP directly established with ultrasound in 2 of 16 cases (12.5%),

No findings were detected in 9 of 16 cases (56.25%).

Management in symptomatic PUL after establishing the diagnoses of Abortus spontaneous or Abortus imminens proceeded ordinarily.

In the context of PUL and EP zero mortality has been reported.

Discussion

In our material sonographic detection of EP in PUL was successful as follows: evident EP sonographic structures were recorded in one of each eight cases of EP, suspect sonographic signs of EP were visualised in less than one-fifth of EP cases and no signs of EP were detected in more than one half of cases with EP.

In the evaluation of our results we start from the fact that the main goal of PUL management is – firstly, an early detection and removal of non-ruptured EP to prevent a pregnant woman from any life and health threat. Secondly, it enables the fastest detection of spontaneous abortion altogether with fetal remains removal, which helps to avoid possible complications. It also ensures suitable therapy in threatened abortion by detection of intrauterine pregnancy in clinical symptomatology.

The basic diagnostic examinations in our PUL management were: sonography examination and β -hCG level measurement. Some authors use also the progesterone level assessment. EP and spontaneous abortion risk factors can be taken into consideration as well.

Sonographic examination

In PUL, the assessment of the structure and the area of uterine cavity, or the gestational sac and adnexal findings, are the most important. The examination results can be also influenced by overall uterus assessment as well as the ovaries and the Pouch of Douglas assessments. Therefore, the intimate knowledge of sonographic examination in the first trimester seems to be inevitable (14).

Uterine cavity during normal pregnancy contains – progressively – the following structures: gestational sac at 4 completed weeks of gestational age, yolk sac at 5 completed weeks of gestation age, fetal pole and fetal cardiac activity at 6 completed weeks of gestational age and separated amniotic fluid and celomic cavity with yolk sac at 7 completed weeks of gestational age.

In SAB, the thickened endometrium or various echogenic materials are displayed in the uterine cavity. If thickness of these structures is less than 15 mm (according to some authors even less than 8 mm), it is the case of complete SAB. If it be to the contrary, it is the case of incomplete SAB. However, by sonographic signs of complete abortion, EP cannot be excluded as well (on condition that intrauterine pregnancy was not established before).

Threatened abortion is displayed as normal pregnancy in the cavity but vaginal bleeding and/or pain in lower abdomen are present clinically. If the gestational sac is bigger than 20 mm as well as it is empty, it is an afetal pregnancy. Subchorial haematoma occurs approximately in one-fifth of cases. It is the non-significant sonographic finding and its size is of no prognostic significance. On the other hand, the detection of the fetal heart activity means a good prognostic sign for threatened abortion.

In EP, sonographic finding in the uterine cavity with no “classical” gestational sac can be variable. It can be a case of trilinear endometrium without extended cavity or with the liquid collection. The liquid can extend the entire cavity in slit-shaped structure or creates only a small spherical cavity, analogous to the gestational sac. With chorion not present, the cavity edges are not markedly echogenic. High display resolution of down-to-date ultrasound appliances consequently enables to distinguish this small cavity from the gestational sac. Therefore, so-called pseudo-gestational sac tends to be an outmoded term and should be in no use (4).

The analysis of our sonographic findings in uterine cavity in PUL shows that the least problematic, which means correctly positive, is the establishment of a normal intrauterine gestational sac in the case of threatened abortion. False negativity occurs in cases of early SAB when gestational sac remains looking more like liquid collection and detritus in EP. On the other hand, false positiveness (incorrect establishment of SAB) can occur in EP in case that the uterine cavity is extended more and it is with heteroechoic content. Variability of the uterine cavity findings in EP does not allow us to establish any pathognomic sonographic picture that is typical for EP.

Adnexal masses in PUL occur only in the case of EP. In principle, there are three types of possible sonographic findings:

1) Blob sign is an inhomogeneous mass in the adnexal region adjacent to the ovary moving separately from the ovary. (Blob is a sort of amoebic creature from the film of the same name.)

2) Bagel sign – a mass with a hyper-echogenic ring around the ectopic gestational sac in the adnexal region. (Bagel is a sort of ring-shaped cake.)

3) Gestational sac with a fetal pole (with or without cardiac activity), detected directly in the adnexal region (13).

Our sonographic material assessment proves that false positiveness (the adnexal masses in intrauterine pregnancy) is a rare case. It is mostly connected with chronic inflammation process in the adnexal region or with the ovarian cyst (see below). On the other hand, false negative adnexal masses in EP occur relatively often. It is probably caused by the fusion of a bagel sign or a blob sign with the intestinal echogenicity.

Uterus, in different kinds of PUL, is of no markedly different size as it is the case of early pregnancy. However, the structural changes, e.g. in myomati uterus, can deform uterine cavity shape and to complicate its content assessment.

Our assessment adverts mostly to the problematic detection of intrauterine gestational sac in uterus structures and its cavity deformities in the case of pregnancy in the myomati uterus. Ovary can directly contain a gestational sac in ovarian EP. In PUL with high risk of EP a scan of corpus luteum can be of help because in 85 % of EP cases it is located at the same side as EP (4).

Ovarian cysts in the early pregnancy are presumed to be physiological and resolve spontaneously. Therefore, it is assumed that the examination of ovaries in this period is of limited significance (7). However, the case of ovarian EP detected by us showed a great significance of precise ovarian sonographic examination in PUL.

β -hCG

Measurements of human chorionic gonadotrophin level and transvaginal sonography belong to the basic examination methods in PUL management. There are several ways how to measure β -hCG level. The basic principle is aimed to the so-called discriminatory zone establishment. Subsequently, the establishment of so called β -hCG ratio is necessary. The following step in this approach is the evaluation of a curve for β -hCG levels, which means time-course monitoring of its concentration in blood. The most modern method is the assessment of β -hCG level by means of mathematical model of regression analysis.

β -hCG discriminatory zone evaluates only one β -hCG measurement. It is such a β -hCG level in which a gestational sac is already displayed in a transvaginal sonography scan. This shows that absence of a gestational sac in the TVS scan in the β -hCG level under the discriminatory zone should mean EP. Various authors present this value between 1000 and 3000 IU/l. From this point of view, it is very surprising to see that for the detection of EP from one β -hCG value – was sensitivity 21.7, 15.2 and 10.9 % and specificity 87.3, 93.4 and 95.2 % in value 1000, 1500 and 2000 IU/l. These results, therefore, show that the discriminatory zone value is no helpful in the diagnostics of EP (10).

However, our findings in PUL management show that after exclusion of SAB, EP was diagnosed in all patients with β -hCG levels under 1000UL/l.

β -hCG ratio uses two values of β -hCG, which represents a ratio of the β -hCG values measured in 48 hours (hCG 48 h/hCG 0 h). For pathological PUL, β -hCG value ratio 0.87 with sensitivity 92.7 % and specificity 96.7 % was established (11).

β -hCG curve records the multiple β -hCG values during pregnancy. The curve with 66 % increase in β -hCG level every 48 hrs is traditionally used for normal development of intrauterine pregnancy. The minimum increase which can still mean viable pregnancy represents 35 % on the curve (17). However, the fall in increase is more connected with viability of pregnancy and does not correspond to its localisation (6). On the other hand, the curve of decrease establishes β -hCG levels for spontaneous abortion. The decrease less than 21 % can mean EP (2).

Mathematical model of regression analysis enables to set the risk of EP by means of computer. Sensitivity for EP in this approach is from 82.8 % (2) to 91.7 % (3). However, it is necessary to verify its use for different populations by prospective multicentric studies (13).

Progesterone

The establishment of progesterone levels in PUL management seems to be controversial. While some of the authors consider the value less than 20 nmol/l to be the prognostic borderline for pathological PUL (6), the others consider this borderline to be a prognostic sign for spontaneous regression of pregnancy with positive predictive value of 97 % (1).

The attempts to find new markers, e.g. CA-125 and creatine kinase were not successful in PUL management (8).

Risk factors

PUL management should consider not only general medical history regarding fertility of a woman (18), but also anamnestically increased risk for the early pregnancy pathology. A previous EP in history can be a risk factor for EP, whereas there is only slight connection with PID. Surgical intervention in pelvis minor outside the tubes, caesarean section including, has no connection with EP (3). In symptomatic PUL (pain and/or vaginal bleeding), enhanced risk for SAB is only in case of massive metrorrhagia (15).

Conclusions

From mortality and morbidity points of view, PUL management in our conditions obtains the results that are comparable to those from advanced countries. We see the possibilities for the improvement in PUL management in the following aspects:

1) Implementation of this diagnosis (even if descriptive) into the current clinical practice. Therefore, diagnostic uncertainty would be emphasized and more caution from EP point of view would be enhanced as well.

2) Establishment of specialized Early Pregnancy Units (EPU). Higher specialization would provide faster as well as more precise diagnosis.

3) Improvement of evaluation of β -hCG levels. Mathematical models for EP prediction would improve diagnostics as well.

4) Improvement in sonographic examination. Implementation of new sonographic markers for EP, eventually for SAB, and improvement of sonographers, skills is necessary. The possibility of certification in the PUL area as well as in the fetal nuchal translucency measurement can be offered here.

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SCIENTIFIC AND CLINICAL INFORMATION

Ocular manifestations of neurofibromatosis 1 – m. Recklinghausen

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Summary

Neurofibromatosis type 1 (NF 1) – morbus von Recklinghausen is an autosomal dominant phacomatosis with variable expression. The gene for NF 1 is located on chromosome 17q11.2. Incidence is 1 in 3500 live births. The diagnosis is made on the basis of clinical manifestations. Diagnosis requires the presence of 2 or more major criteria: 6 or more café au lait spots, 2 or more cutaneous neurofibromas or 1 plexiform neurofibroma, an optic nerve glioma, 2 or more iris Lisch nodules, axillary or inguinal freckling, bony lesions – pseudoarthrosis, sphenoid wing hypoplasia, or a first-degree relative with NF 1.

Key words: NF 1 – Neurofibromatosis 1, optic nerve glioma

Patients and methods

We reviewed group of 10 patients hospitalized at our Ophthalmology Department in the last ten years with the diagnosis of optic glioma. In 5 patients were diagnosed Recklinghausen disease, 1 patient has suspected NF 1. The first presenting sign in all patients was protrusion of the eye bulb. 5 patients underwent resection of the tumor which has proven to be pilocytic astrocytoma in all 5 cases.

Ocular features

NF 1 may affect the iris, optic nerve, retina, bony and soft tissue of the orbit. Lisch nodules are proliferations of melanocytes and fibroblasts in the iris and have no affect the vision, onset is usually in a teenage years. Retinal hamartomas occur in a small percent of patients. Orbital asymmetry is indicative of some degree of hypoplasia of the sphenoid bone, a progressive resorption of the sphenoid wing causing proptosis. Plexiform neurofibromas of the orbit are frequent, they grow along large peripheral and cranial nerves and

plexuses and they extensively encompass the skin and neighbouring subcutaneous and deeper tissues. They look like subcutaneous tumors and the skin over plexiform neurofibroma is thickened and hyperpigmented with excessive hairiness.

Results

The treatment of these patients is mostly symptomatic. Surgery is currently the only treatment option for most of the lesion in NF1 localised in orbit. The progression of the disease in these our patients were stopped. Chemotherapy is helpful to decrease tumor size. Radiation therapy can stimulate the grow of malignant tumors.

Discussion

Optic gliomas are the most frequently identified neoplasm in young patients with NF 1. These visual pathway tumors are found in 15% patients (in our set in 50% of children) and may lead to blindness. Histologically are a pilocytic astrocytomas. The greatest risk for the development of optic pathway tumors in NF1 is during the first 6 years of life. The clinical behavior of optic gliomas is related to their anatomic extent. Isolated to the optic nerve are relatively benign, chiasmal involvement is worse.

Conclusion

The management of patients with NF1 require multidisciplinary clinic care, imaging studies and genetic counselling.

This study was presented on the Meeting of the Slovak Medical Society, on the March 3, 2008 in Bratislava.