Retrospective Observational Study of Ultrasonography for Molar Pregnancy in Nangarhar, Afghanistan

Teaching Assistant Drs. Wahida Ahmady1,
Teaching Assistant Dr. Shah Agha Salehi2
Teaching Assistant Dr. Sayed Azizullah Hashimi3

1 Member of Obs/Gyn Department, Medical faculty, Nangarhar University, Jalalabad, Afghanistan.
2 Member of Microbiology Department, Medical faculty, Nangarhar University, Jalalabad Afghanistan.
3 Member of Radiology Department, Medical faculty, Nangarhar University, Jalalabad Afghanistan.

Abstract

Introduction: The primary aims of this study were to establish what proportion of ultra-sonographic suspected molar pregnancies and to review the features of these scans to help identify criteria that may improve ultra-sonographic diagnosis. This was a retrospective observational study conducted in the Early Pregnancy in Nangarhar University Teaching Hospital over in 2-year period. Cases of ultrasonographically suspected to molar pregnancy or other gestational trophoblastic disease were identified. In addition, cases which were diagnosed on histopathology that were not suspected on ultrasound were also examined. In discrepant cases, the images were reviewed unblended by two senior sonographers. Statistical analysis for likelihood ratio and post-test probabilities was performed. There was a total of 18864 pregnancies during the study period seventy-two women had gestational trophoblastic disease suspected on ultrasound examination (1:262, 0.38%) 53/72 (73.6%) had histologically confirmed gestational trophoblastic disease, Sensitivity was 73.6% with an estimated specificity of 99.7%. 72 molar pregnancies were suspected on pre-op ultrasound; 43/72 of complete moles were suspected on pre-op ultrasound, compared with 16/72 of partial moles. On retrospective review of the pre-op ultrasound images, there were cases that could have been suspected prior to surgery. Detecting molar pregnancy by ultrasound remains a diagnostic challenge, particularly for partial moles. These data suggest that there has been an increase in both the predictive value and the sensitivity of ultrasound over time, with a high LR and post-test probability; however, the diagnostic criteria remain ill-defined and could be improved.

Keywords: Ultrasound, histopathology, hydatidiform, complete mole, partial mole, molar pregnancy

Introduction

Gestational trophoblastic disease (GTD) is a term used for a group of pregnancy-related tumors. These tumors are rare, and they appear when cells in the womb start to proliferate uncontrollably. The cells that form gestational trophoblastic tumors are called trophoblasts and come from tissue that grows to form the placenta during pregnancy. There are several different types of GTD. Hydatidiform moles are benign in most cases, but sometimes may develop into invasive moles, or, in rare cases, into choriocarcinoma, which is likely to spread quickly, but which is very sensitive to chemotherapy, and has a very good prognosis. Gestational trophoblasts are of

particular interest to cell biologists because, like cancer, these cells invade tissue (the uterus), but unlike cancer, they sometimes "know" when to stop.GTD can simulate pregnancy, because the uterus may contain fetal tissue, albeit abnormal. This tissue may grow at the same rate as a normal pregnancy, and produces chorionic gonadotropin, a hormone which is measured to monitor fetal well-being.While GTD overwhelmingly affects women of child-bearing age, it may rarely occur in postmenopausal women

Gestational trophoblastic disease (GTD) comprises a group of disorders including complete (CM) and partial (PM) molar pregnancies, invasive moles, choriocarcinomas and placental site trophoblastic tumors. Molar pregnancies are categorized as complete or partial, occurring 1:1000 and 3:1000 pregnancies in the UK, respectively.1 The incidence of molar pregnancy is rising in the UK and Western Europe, in part due to an increasing number of women having pregnancies at a later age.
early embryonic demise, an enlarged uterus, early preeclampsia, hyperthyroidism and abdominal distension3.The characteristic ultrasound appearance of hydatidiform mole was first described by Donald in the 1960s as a ‘uterus full of dots’ or a ‘snowstorm’. This traditional description is of the late features of the disease that are seen in the second trimester. Over the last 20 years in the UK, increasingly sensitive home pregnancy tests and Early Pregnancy Units (EPUs) equipped with transvaginal ultrasound have brought the clinical presentation forward to the first trimester, when the symptoms and ultrasound findings are more subtle. Concurrently, there has been a move away from routine surgical treatment of +miscarriage and increasing use of expectant and medical treatments with no histological examination of pregnancy tissue. Although a pregnancy test can be performed three weeks after a miscarriage to exclude persistent GTD, the lack of diagnosis denies women appropriate follow up in subsequent pregnancies. If a woman is known to have had a molar pregnancy, her follow-up is coordinated by our UK regional GTD units and she has an increased risk of a recurrent mole in future pregnancies, particularly after a CM.7 Ultrasound identification of a possible molar pregnancy allows women to choose surgery over other management options allowing histopathological examination of pregnancy remains. The primary aims of this study were to establish (a) what proportion of ultrasonically suspected molar pregnancies were proven on histological examination and (b) what proportion of histologically diagnosed molar pregnancies were identified by ultrasound pre-operatively. The secondary aim was to analyze the features of the pre-op scans to help identify criteria that may improve ultrasound diagnosis.

Methods

This was a retrospective observational study conducted in the Nangarhar University Teaching Hospital. Women accessed to this Hospital as self-referred patients, referrals from general practitioners, midwives, fetal medicine unit or the emergency department. Clinical and ultrasound data were collected prospectively and stored electronically. All patients had a clinical assessment and transabdominal and transvaginal ultrasound performed by Sonologist and Gynecologist sonographers working in the Nangarhar University Teaching Hospital in Radiology and Gynecology departments. If the uterus was enlarged, this was supplemented just by transabdominal approach. The ultrasound criteria for suspecting molar pregnancy were cystic changes, irregularity, or increased echogenicity in the decidua, chorionic tissue or myometrium. The ultrasound criteria for suspecting malignant GTD were a hypoechoic or heterogeneous, predominantly solid tumors within the uterine cavity in the presence of a positive pregnancy test.

Inclusion criteria for the primary aims were an ultrasound scan in the first trimester with the diagnosis of a suspected molar pregnancy or other GTD confirmed at Nangarhar University Teaching Hospital over 2 year period, January 2019 to December 2020. Unblended, retrospective review of USS images was performed by two senior sonologists Dr Salehi, Dr Hashimi and one Gynecologist Drs Ahmady. Statistical analysis for likelihood ratio and post-test probabilities was performed using SPSS programed.

Results

There were a total of 18864 pregnancies during the study period of which 72 had GTD on ultrasound examination (1:262, 0.38%); 53/72 (73.6%) had histologically confirmed GTD, including a patient with a pregnancy that was unclassifiable histologically, thought to be most likely to be a non-molar pregnancy, but as an atypical mole could not be excluded, she was followed up as per the molar pregnancy protocol; 16/72 (22.2%) were non molar miscarriages on histological examination, 1/72 had ongoing pregnancies in which the placental or decidual cysts resolved by the end of the first trimester and they delivered normal babies at term, 2/72 miscarried spontaneously with no tissue available for histology and 1/72 patients had their surgery in the private sector with no histology results available locally. There were 44 cases of GTD diagnosed histologically with no documented suspicion of the diagnosis on the pre-operative ultrasound. One of these patients presented with abnormal vaginal bleeding at the age of 54 years, was not known to have a positive urinary pregnancy test and the diagnosis of choriocarcinoma was made by outpatient endometrial sampling. Another had a partial molar tubal ectopic pregnancy. Ultrasound 0(0) Details of the histological subtypes of GTD are shown in Table 1. Assuming the approximation that there was no additional GTD in patients with negative scans who did not have histological tissue for analysis, the sensitivity of ultrasound was 73.6% with a specificity of 99.7% . Considering molar pregnancies alone, 43/72 of complete moles (CM) were suspected on ultrasound preoperatively, compared with 16/72 of partial moles (PM). Overall, 102/143 molar pregnancies were suspected on pre-op ultrasound.

Table 1. Histological subtypes of gestational trophoblastic disease 2019-2020 inclusive

U/S for molar pregnancy	Complete mole	Partial mole	Invasive mole	choriocarcinoma	Placental site tumor	unclassifiable
Suspected on USS(=72)	43	16	0	1	1	1
Unsuspected on USS(n=18)	3	14	0	0	1	0
Total(n=90)	46	30	0	1	2	1

We looked back at examples of the ultrasound images of six of the eight patients with false negative ultrasound scans who had complete moles (Figure 1). Two patients only had scans in the fetal medicine unit and their ultrasound images were not available for review. The cases shown in Figure 1(a) and (b) demonstrated cystic changes in the chorionic tissue typical of molar

pregnancies. In case 1(a), the Gynecologist who performed the scan commented that tissue should be sent for histological examination, but was not explicit in stating that this was to check for GTD. Figure 1(c) to (f) shows more subtle changes; 1(c) shows small cysts in the chorionic tissue and a relatively high proportion of trophoblast for a small gestational sac. 1(d) and (e) shows abundant chorionic tissue with loss of the normal sac-like architecture. Figure 1(f) showed a small irregular gestational sac only and we were unable to see any features that could indicate a complete mole.

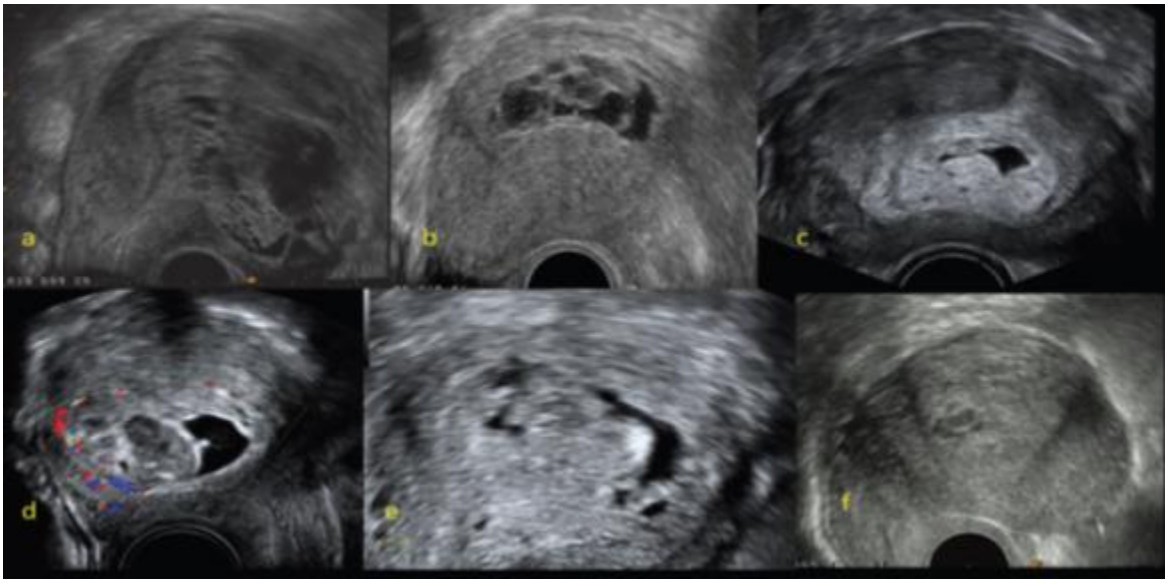

Figure 1. Missed complete moles (false negative ultrasound scans).

There were 33 cases of partial molar pregnancies that were not recorded as having been suspected on pre-operative ultrasound. One of these was the tubal mole. On pre op ultrasound, this was a 3 cm, predominantly solid ectopic pregnancy. The trophoblast appeared echogenic, but otherwise it was unremarkable (Figure 2).

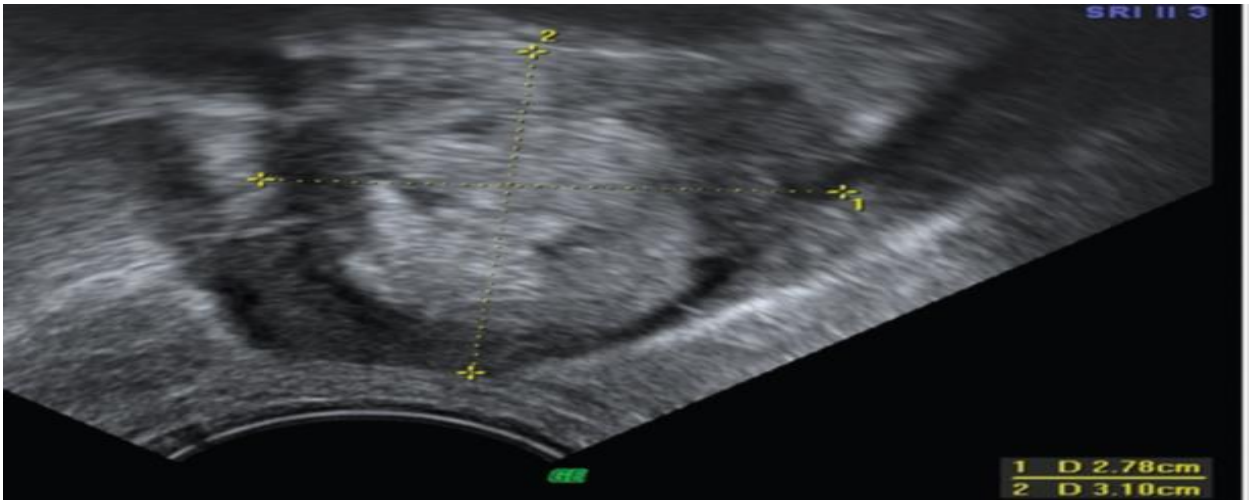

Figure 2. Tubal ectopic partial molar pregnancy.

Thirteen cases of PM were referred from the Fetal Medicine Unit and there were six of these with no images available to review. Of the remaining 26 cases, reviewing the images retrospectively and independently, 8/26 had USS features that could have indicated a partial mole (Figure 3). However, the reviewers disagreed in six cases (k¼0.115) indicating a generally poor strength of agreement.

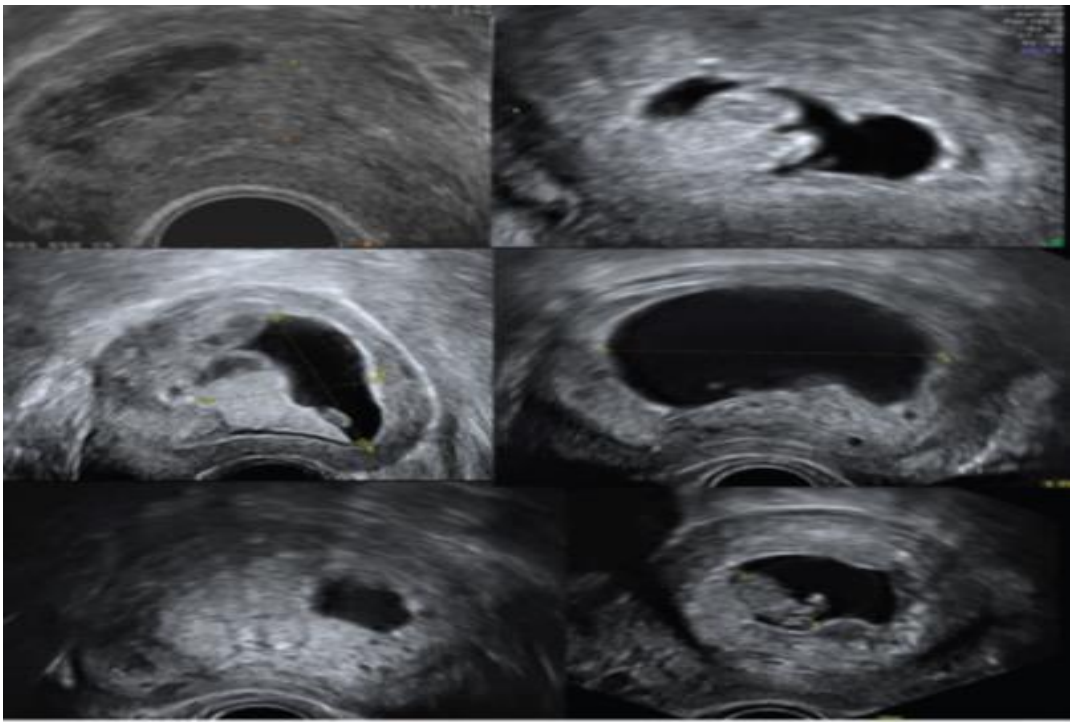

Figure 3. Missed partial molar pregnancies (false negative ultrasound scans).

Discussion

This study has shown that just over half of the pregnancies, we suspect to be molar on ultrasound are proven to be so, and that we are able to detect a higher proportion of molar pregnancies by pre-operative ultrasound than previously reported in the literature. An overview of previous studies showed that 533/1210 (44%) of molar pregnancies were suspected on USS pre operatively, with the US sensitivity form CM moles being much higher than for PM (Table 2).The overall increase in ascertainment in the current study was due to a lower proportion of PM in our population compared with other studies. This may reflect an increasing use of non-surgical treatment of miscarriage over time, but our data were fairly consistent year on year. We treat approximately 20% non-surgically, which may be higher than in some other units – and we do not routinely try to collect tissue from non-surgically managed miscarriages for histopathological examination. This means that unsuspected cases of PM may have been missed as they were treated non-surgically. As CM shows a more pronounced increase with age,14 but these data were not available for comparison. Since modern transabdominal and transvaginal ultrasound has been used routinely for the assessment of early pregnancies, the proportion of molar pregnancies suspected preoperatively has risen. One of the strengths of our study was that we were able to identify and follow-up pregnancies that were thought could be molar on ultrasound and establish whether the diagnosis was proven on histology so as to assess the value of a positive scan. This is important

for sonographers and clinicians so that we can counsel our patients regarding the odds of molar pregnancy before they choose the treatment of their miscarriage. who found a positive predictive value of 48% for the diagnosis of molar pregnancy, previous studies have only looked at cases where the diagnosis of a molar pregnancy was made histologically to give an estimate of sensitivity? It would be interesting to see whether our data are replicated in other units with a different clinical set ups, staffing and degrees of supervision, to see whether this pattern of diagnosis is consistent across modern practice. Our study was limited by the retrospective analysis of data. We assumed that all pregnancies that were thought to be molar were explicitly stated as such in the ultrasound reports. It is possible that our Gynecologist sonographers may have recommended surgical management of miscarriage, but not made it expressly clear in the report that this was because they suspected an underlying molar pregnancy and wanted the remains to be examined histologically. We also had to assume that there was no additional GTD in patients with negative scans who did not have histological tissue for analysis. This was likely to be the case for malignant or invasive GTD, but it is quite possible that there were some cases of molar pregnancy that resolved with expectant or medical management of miscarriage without ever being suspected or detected. Without histopathological examination of all miscarriage tissue, the true false negative rate of ultrasound is impossible to gauge .Can we improve ultrasound detection of molar pregnancy? We have no diagnostic criteria that have been subject to testing for accuracy or reproducibility examined USS images of proven moles in an to attempt to grade the cystic changes in the placenta and vascularity; they found that PM were more likely to have recognizable embryonic and extra embryonic structures, were more vascular and less likely to consist of cystic placental tissue with no recognizable sac.

Our retrospective, unblended review of images showed that there were some cases of CM that could have been suspected by more experienced sonographers on USS prior to surgery, due to abundant chorionic tissue with loss of the normal architecture of the gestational sac, but that the main diagnostic difficulty is in distinguishing PM from uncomplicated first trimester miscarriage (i.e. early embryonic demise). Without a prospective study using predefined assessment criteria, the diagnostic criteria will never be rigorously assessed. Do we need to improve ultrasound detection of molar pregnancy, particularly PM? Will it alter how the miscarriage is managed? There is an ongoing debate in the UK about the financial cost and value of histological examination of the tissue obtained

from surgical treatment of miscarriage.15 What is the value of knowing the diagnosis of PM when it is easy to do a urinary pregnancy test after a miscarriage to check for the rare cases of persistent GTD? In the UK, it is no longer advised that women wait six months before conceiving again after a PM, so delaying a pregnancy is no longer a potential reason to check histology, and the risk of a CM after a PM is 0.1%, as recurrent CM is almost exclusively a problem of CM.7 It may be that knowledge of an underlying PM needlessly increases women's anxiety in future pregnancies, when the risk of recurrence is very low. Making the diagnosis could also have the opposite effect, reducing anxiety; however, there is no data available from which to draw a conclusion as to whether there is any psychological benefit of knowing the diagnosis.

Conclusion

Detecting molar pregnancy by ultrasound remains a diagnostic challenge, particularly for PM. These data suggest that there has been an increase in both the predictive value and the sensitivity of ultrasound over time; however, the diagnostic criteria remain ill defined. Awareness of the possibility of molar pregnancy prior to management of miscarriage will guide treatment and allow appropriate follow-up. The recent increase in non-surgical management of miscarriage may result

in missed cases but this may well be almost exclusively in PM where the value of a diagnosis is less clear.

References

1. Seckl MJ, Sebire NJ and Berkowitz RS. Gestational trophoblastic disease. Lancet 2010; 376: 717–729.
2. Lybol C, Thomas CMG, Bulten J, et al. Increase in the incidence of gestational trophoblastic disease in The Netherlands. Gynecol Oncol 2011; 121: 334–338.
3. Ngan HY, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 2015; October(131 Suppl 2): S123 S126.
4. Donald I. Use of ultrasonics in diagnosis of abdominal swellings. Br Med J 1963; 2: 1154 1155.
5. Robinson DE, Garrett WJ and Kossoff G. The diagnosis of hydatidiform mole by ultrasound. Aust N Z J Obstet Gynaecol 1968; 8:74–78.
6. Donald I and Brown TG. Demonstration of tissue interfaces within the body by ultrasonic echo sounding. Br J Radiol 1961; 34: 539–546.
7. Eagles N, Sebire NJ, Short D, et al. Risk of recurrent molar pregnancies following complete and partial hydatidiform moles. Hum Reprod 2016; 31: 1379.
8. Fine C, Bundy AL, Berkowitz RS, et al. Sonographic diagnosis of partial hydatidiform mole. Obstet Gynecol 1989; 73: 414–418.
9. Lazarus E, Hulka C, Siewert B, et al. Sonographic appearance of early complete molar pregnancies. J Ultrasound Med 1999; 18: 589–594; quiz 95–96.
10. Shanbhogue AK, Lalwani N and Menias CO. Gestational trophoblastic disease. Radiol Clin N Am 2013; 51: 1023–1034.
11. Sebire NJ, Rees H, Paradinas F, Seckl M and Newlands E. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancies. Ultrasound in Obstetrics and Gynecology 2001; 18: 662–665.
12. Johns J, Greenwold N, Buckley S, et al. A prospective study of ultrasound screening for molar pregnancies in missed miscarriages. Ultrasound Obstet Gynecol 2005; 25: 493–497.
13. Fowler DJ, Lindsay I, Seckl MJ and Sebire NJ. Routine preevacuation ultrasound diagnosis of hydatidiform mole: experience of more than 1000 cases from a regional referral center. Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology 2006; 27: 56–60.
14. Kirk E, Papageorghiou AT, Condous G, et al. The accuracy of first trimester ultrasound in the diagnosis of hydatidiform mole. Ultrasound Obstet Gynecol 2007; 29: 70–75.
15. Savage JL, Maturen KE, Mowers EL, et al. Sonographic diagnosis of partial versus complete molar pregnancy: a reappraisal. J Clin Ultrasound 2017; 45: 72–78.
16. Sebire NJ, Foskett M, Fisher RA, et al. Risk of partial and complete hydatidiform molar pregnancy in relation to maternal age. BJOG 2002; 109: 99–102.
17. Alsibiani SA. Value of histopathologic examination of uterine products after first-trimester miscarriage. Biomed Res Int 2014.
18. Jackie A. Ross, Alina Unipan, Jackie Clarke, Catherine Magee and Jemma Johns,Ultrasound diagnosis of molar pregnancy

19. Wang CM, Dixon PH, Decordova S, et al. Identificationof 13 novel NLRP7 mutations in 20 families with recurrent hydatidiform mole; missense mutations cluster in the leucine-rich region. J Med Genet 2009;46:569–75.

20. Deveault C, Qian JH, Chebaro W, et al. NLRP7 mutations in women with diploid androgenetic and triploid moles: a proposed mechanism for mole formation. Hum Mol Genet 2009;18:888–97.
21. Tidy JA, Hancock BW, Newlands ES. The management of gestational trophoblastic neoplasia. Royal College of Obstetricians and Gynaecologists (RCOG) clinical guideline No. 38. London: RCOG Press; 2004.
22. Seckl MJ, Gillmore R, Foskett M, et al. Routine terminations of pregnancy–should we screen for gestational trophoblastic neoplasia? Lancet 2004; 364:705–7.
23. Berezowsky J, Zbieranowski I, Demers J, et al. DNA ploidy of hydatidiform moles and nonmolar conceptuses: a study using flow and tissue section image cytometry. Mod Pathol 1995;8:775–81.
24. Fisher RA, Newlands ES. Gestational trophoblastic disease. Molecular and genetic studies. J Reprod Med 1998;43:87–97.
25. Castrillon DH, Sun D, Weremowicz S, et al. Discrimination of complete hydatidiform mole from its mimics by immunohistochemistry of the paternally imprinted gene product p57KIP2. Am J Surg Pathol 2001;25:1225–30.
26. Santos-Ramos R, Forney JP, Schwarz BE. Sonographic findings and clinical correlations in molar
pregnancy. Obstet Gynecol 1980;56:186–92.
27. Gemer O, Segal S, Kopmar A, et al. The current clinical presentation of complete molar pregnancy. Arch Gynecol Obstet 2000;264:33–4.
28. Jauniaux E. Partial moles: from postnatal to prenatal diagnosis. Placenta 1999;20:379–88.
29. Buli_c M, Bistricki J, Podobnik M, et al. Evacuation of a hydatidiform mole with ultrasonic guidance.Jugosl Ginekol Opstet 1983;23:85–8.
30. Maymon R, Schneider D, Shulman A, et al. Serial color Doppler flow of uterine vasculature combined with serum beta-hCG measurements for improved monitoring of patients with gestational trophoblastic disease. A preliminary report. Gynecol Obstet Invest 1996;42:201–5.
molar pregnancy. BJOG 2003;110:22–6.
31. Gottesfeld KR, Taylor ES, Thompson HE, et al.
Diagnosis of hydatidiform mole by ultrasound. Obstet Gynecol 1967;30:163–71.
32. Kohorn EI, Blackwell RJ. The diagnosis of hydatidiform mole by ultrasonic B-scanning. J Obstet Gynaecol Br Commonw 1968;75(1):014–8.
33. Nikolic B, Lukic R. Choriocarcinoma – postdisease ultrasonographic
findings. *Int J Gynecol Cancer* 2004; 14: 677–679.