

# Assessment of a diagnostic value of histopathological test results in miscarriages, depending on a treatment method applied

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## SUMMARY

**Introduction.** The miscarriage rate among patients who know they are pregnant, is roughly 10 to 15%. An empty gestational sac or a missed or incomplete abortion are all indications for either invasive or pharmacological treatment. In the process uterine products of conception are being examined by histopathologic. The aim of this study was to determine the diagnostic value of miscarriage tissue acquired as the result of either pharmacological or invasive treatment.

**Material and methods.** In this retrospective study we analysed history of 258 patients hospitalised in 2016 within the 2nd Dept. of Obstetrics and Gynaecology, Wrocław Medical University, with an initial diagnosis of missed abortion or empty gestational sac. We compared the diagnostic value of histopathological reports on the uterine products of conception collected either after pharmacological treatment or after invasive curettage. We analysed collected data using statistical models.

**Results.** Among the analysed patients 232 (92,6%) underwent pharmacological treatment which was the only treatment resulting in completion of miscarriage in 61 patients (23,7%), versus 171 patients (68,9%) who were qualified for curettage of the uterine cavity due to insufficient emptying of the uterine cavity after pharmacological treatment. 16 (6,2%) patients underwent curettage without previous pharmacological treatment. Uterine products consisting of both fetal and maternal tissue has been obtained in 80 cases (35%) after only pharmacological treatment vs in 133 (52%) after curettage. Nondiagnostic histopathological material was observed in 38 patients (15%) after only pharmacological treatment vs in 6 patients (2%) after curettage. Observed differences were statistically significant.

**Conclusions.** Pharmacological treatment of miscarriages has many advantages but it does not guarantee to provide diagnostic material for future histopathological analysis. In all cases of insufficient emptying of the uterine cavity, the invasive approach - curettage - should be advised in order to obtain good quality tissue samples for histopathological analysis.

**Key words:** missed abortion; medical management; surgical management; histopathology

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## INTRODUCTION

Miscarriage is one of the most common diagnoses in the first trimester of the pregnancy. It is estimated that early fetal demise occurs in 10 to 15% of all pregnancies below the 12 gestational week, so the scale of this problem is significant [1,2]. Miscarriages can be classified as spontaneous - when bleeding occurs resulting in expulsion of an ovum from the uterus either as a whole (complete spontaneous abortion) or with retained tissues left (incomplete spontaneous abortion). A diagnosis of missed abortion is based on diagnostic imaging and laboratory tests - when no foetal heart function is noted, its CRL is > 7 mm in the ultrasound scan and/or when chorionic gonadotropin levels drop. Hydrovum is indicated by lack of foetal structures in the gestational sac (GS) of diameter exceeding 25 mm in the ultrasound scan [3].

Traditionally, a diagnosis of an incomplete or missed abortion, or of an empty gestational sac, was an indication for curettage. The surgical treatment, despite being an invasive procedure, was mainly conducted to limit complications associated with retained trophoblast tissues remaining in the uterus, including infections of the reproductive organs, systemic infection (sepsis) or sudden haemorrhages [4].

With improvement in imaging techniques used during early pregnancy stages, and in clinical pharmacology, as well as with attempts to introduce minimally invasive treatment of comparable effectiveness, current management of diagnosed miscarriage cases changed. Currently, several therapeutic options are available: traditional surgical evacuation of pregnancy tissues from the uterus, pharmacological treatment with vaginal prostaglandin analogues, progesterone receptor antagonists, selective oestrogen receptor modulators or cytotoxic

drugs, or, finally, observation. Effectiveness of complete cleaning of the uterus depends on the treatment method used. According to the literature data, the effectiveness of the pharmacological treatment ranges within wide limits from 13 to 94%, depending on a type, dose and regimen (single or repeated dose) of the drug used [5–8]. The expectant management also results in achieving the therapeutic objective - emptying of the uterine cavity of trophoblast tissues in 81% of cases of failed early pregnancy on average, including 91% of incomplete spontaneous abortion cases, 76% missed abortions, and 66% of patients diagnosed with the empty gestational sac [9] - however, it raises controversies due to a risk of infection.

In the literature, opinions about viability of routine histopathological examination of material obtained from the uterus at the early pregnancy stage differ [10–12]. Some authors, similarly as in our centre, recommend histopathological examination to be conducted in each case [10,11]. The microscopic pathological examination allows identification of tissues removed from the uterus, including those of foetal origin, and of trophoblast pathologies, facilitates further genetic diagnostics for chromosomal aberrations in the examined material, may indicate a need to conduct additional genetic tests in parents, and when no villi are found in the examined material from the curettage of the uterine cavity, together with other results, directs diagnostic process towards a search for ectopic pregnancy [11].

## STUDY OBJECTIVE

The aim of the study was the assessment of a diagnostic value of histopathological results in cases of miscarriages, depending on a method used to obtain the tissue material, i.e., following pharmacological induction of miscarriage or curettage of the uterine cavity.

## MATERIAL AND METHODS

A retrospective study was conducted on medical records of 258 patients hospitalised in 2016 at the 2nd Department and Clinic of Obstetrics and Gynaecology in Wrocław and diagnosed with missed abortion or empty gestational sac. Patients in the first gestational trimester when admitted to the ward were also enrolled into the study. The patients underwent pharmacological or surgical treatment, depending on individual medical indications and taking into

account patient's wishes. In the pharmacological treatment, misoprostol at a dose of 800 µg/day was used, 2 x 400 µg at a 6-hour interval. On the second day, following ultrasound evaluation, when any post-miscarriage residues of > 11 mm were found in the uterine cavity, being a measure of the treatment ineffectiveness, the regimen was repeated. When the pharmacological treatment was ineffective on the third day of treatment, these patients underwent curettage of the uterine cavity. The tissue material obtained at each treatment stage was delivered to the Pathomorphology Department for histopathological examinations. The histopathological evaluation was performed according to a standard procedure, after fixing the tissue material in the 10% formaldehyde solution, with slides stained with haematoxylin and eosin. The results of delivered tests taken into account presence of foetal tissues in the examined material, villi characteristics, presence of mother tissues and other structures not providing important diagnostic information - blood clots, or autolysed tissues.

Data obtained from medical records were statistically analysed for age, parity, pregnancy age, diagnosis, treatment method, and method used to obtain material for a histopathological analysis, taking into account the treatment method. The results of histopathological examinations were evaluated in terms of their diagnostic value, and the obtained data was classified into one of three groups: 1. mother and foetal tissues, villi, parts of a foetus, fragments of a chorion found in the examined material, 2. only mother tissues found - fragments of the decidua without villi, 3. non-diagnostic structures found in the examined material - autolysed tissues, blood clots. Statistical analyses were performed in the STATISTICA application using the Chi2 Pearson test.

## RESULTS

In the studied group, consisting of 258 women, empty gestational sac was found in 34 (13.17%) and missed abortion was diagnosed in 224 (86.83%) of patients. The mean age was 34 years (from 21 to 42 years). The median was 1.96 (from 1 to 6) for parity and 9 gestational weeks for the pregnancy age. In 232 (92.6%) patients pharmacological treatment was initiated, while 16 (6.2%) underwent surgical treatment as a treatment of choice. In 61 (23.7% of all) patients pharmacological treatment was successful, and in 171 (68.9%) of women cu-

rettage of the uterine cavity was required due to incomplete effectiveness of the pharmacological treatment. In a group of histopathological results obtained for material collected after pharmacological treatment, results of full diagnostic value - containing material from a fetus and a mother - was obtained in 80 cases, representing 35% of subjects, while in the group undergoing curettage such results were obtained in 133 cases, corresponding to 52%. A histopathological result containing material only from a mother was obtained from 49 (19%) and 59 (23%) women following the pharmacological treatment and curettage, respectively. Non-diagnostic results were found in 38 (15%) patients undergoing pharmacological treatment and in 6 (2%) after a surgical emptying of the uterine cavity. A difference between these results is statistically significant, as shown by the Chi2 Pearson test, with  $p=0.000$ . In 90 women no material was obtained for histopathological examinations following the pharmacological treatment, and they represent a significant group of 35% of women undergoing the pharmacological treatment. In 104 cases (40% of all patients) in which a full diagnostic result was obtained following curettage of the uterine cavity, no result or a result of a low diagnostic value was obtained following pharmacological treatment, and only 11% women had consistent results in these cases. After curettage of the uterine cavity, the fully representative material was obtained in 52% of cases. In the studied material, 3 (1.1%), 2 (0.77%) and 1 pregnancies with hydatidiform mole, complete mole, and partial mole were found, respectively. Patients with this diagnosis underwent the pharmacological treatment, which ended with curettage of the uterine cavity due to incomplete effectiveness of the pharmacological treatment. All examined material came from curettage, as no material for histopathological examinations was obtained following the pharmacological treatment.

## DISCUSSION

The pharmacological treatment in patients diagnosed with spontaneous abortion, including missed abortion and empty gestational sac, has many advantages versus the surgical treatment, as it is less invasive, more acceptable for patients, with a low rate of short- and long-term complications associated with the procedure itself and the required anaesthesia [13,14]. However, on the other hand, it is associated

with a longer period of bleeding, longer hospitalisation, a higher rate of emergency procedures resulting from reaction to the applied treatment, and lower effectiveness versus the surgical treatment, in consequence requiring supplementation with instrumental control of the uterine cavity [13–15]. An analysis of cases of treatment for incomplete abortion conducted by Greek researchers showed that the pharmacological treatment is less effective in 66% cases, vs. 100% of cases of complete emptying of the uterine cavity [18]. The similar relationship was observed in our own studies, as the pharmacological treatment applied, using Misoprostol, required subsequent curettage of the uterine cavity to evacuate retained tissues for a high percentage (68.9%) of all cases.

The histopathological examination of the material collected after abortion aims at identifying trophoblast pathologies, including gestational trophoblastic disease, hydatidiform mole, or chorionic cancer. In our analysis, pregnancies with hydatidiform mole represented 1.1% of all cases, and this is consistent with results of other authors [17,18]. According to the literature, the histopathological examination is useful also in the diagnostic process, as it helps to diagnose a location of the early pregnancy when its location is unknown, or, less frequently, suggests chromosomal anomalies in the foetal material as a cause of the abortion [11]. Despite this fact, not all authors agree that obligatory pathological examinations are justified in each case of abortion. In the study of Heath et al., a ratio of anomalies found in the examined tissue material was so low that the authors of that report are of the opinion that the histopathological examination should be performed only in women with uncertain diagnosis, when the amount of the tissue material is not correlated with an earlier diagnosis, or when the obtained tissues macroscopically suggest other pathology than previously assumed, e.g., degeneration of villi [12]. A disadvantage of the above approach is a possibility that important pathologies will remain undiagnosed, and in consequence, there is a risk for patients that they will not receive the targeted therapy or it will be delayed. According to other authors, including *Royal College of Obstetricians and Gynaecologists*, the histopathological examination still remains a necessary part of the diagnostic and therapeutic procedures [10,16]. This results from the importance of the diagnosis concerning the group of trophoblast diseases, and differences in frequency of their occurren-

ce, varying from 0.13 to 18% according to different authors [11,13,16,17]. At our centre, the histopathological examinations are performed in each case of abortion in which tissue material was obtained, regardless of the initial diagnosis, macroscopic evaluation or clinical symptoms. In this study it was confirmed that the representative material for histopathological examinations cannot be obtained for each case of the pharmacological treatment, while it occurred only sporadically after curettage of the uterine cavity. The diagnostic tissue material was found only in 50% of women undergoing the pharmaceutical treatment (and villi were found in 31% of them), while for curettage of the uterine cavity tissue material was present in 96% of cases. Petersen presented similar results in his report, and he obtained a diagnostic result of the histopathological examination of material from the pharmaceutical treatment only in

22.8% of cases, and in all cases the material contained villi. Different results were found in the report by Heath et al., in which the representative material was obtained in the majority (99.5%) of patients treated pharmacologically. However, in these cases the drug regimen was different because it involved a combined therapy (Misoprostol and Mifepriston).

## CONCLUSIONS

Despite its numerous advantages, pharmacological treatment for abortions does not guarantee obtaining representative tissue material for histopathological examinations, and this should be considered when this type of treatment is proposed. In cases of incomplete expulsion of the tissues from the uterine cavity, instrumental control of the uterine cavity must be performed to obtain tissue material for histopathological evaluation.

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