

Frozen section of uterine curetting in excluding the possibility of ectopic pregnancy - a clinicopathologic study of 715 cases

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Summary

Introduction: To investigate the utility of frozen section of uterine curetting in excluding the possibility of ectopic pregnancy (EP). **Materials and Methods:** A retrospective analysis of 715 curetting records in the present hospital from July 1999 to May 2009 was obtained. All specimens were processed routinely with frozen section and paraffin section. **Results:** Of 715 cases, frozen section analyses were discordant in 33 cases (4.6%), including 32 cases under-diagnosed, and one case over-diagnosed, compared with the final diagnoses. Frozen section had a sensitivity of 92.6%, specificity of 99.6%, and frozen section accuracy rate of 95.4%. **Conclusions:** Frozen section is a useful and rapid method to differentiate EP from intrauterine pregnancy.

Key words: Uterin curetting; Ectopic pregnancy; Frozen section.

Introduction

Ectopic pregnancy (EP) is a potentially serious threat to women's health, which may lead to catastrophic presentation or death in case of ruptured EP. Commonly, a diagnosis of "suspicion of EP" is suggested by pelvic examination, β -ultrasonography, and serial serum β -subunit human chorionic gonadotropin (β -HCG) titers, but sometimes when patients presented with mild abdominal pain and minimal vaginal bleeding, β -HCG and β -ultrasonography cannot assist in differentiating threatened abortion from EP, then curettage may serve to exclude the possibility of EP. For this reason, if villi are not identified by immersing curettings in water, the curettings would be submitted to histopathology diagnosis and the patient would be admitted until the site of pregnancy is determined. Thus the pathology diagnosis is essential for further management. However, it may take two to three days to make the final pathology diagnosis. The waiting period is not only a burden to the patient and her relatives, but a waste of medical resources. Frozen section takes 20 minutes after curettage, which is much quicker than paraffin section. If the frozen section analysis of uterine curetting is as reliable as that of paraffin section, the problem can be solved. Previous studies [1-4] have demonstrated the accuracy of uterine curetting, but they have been studied only in small series and the authors paid more attention on clinical issues. In order to investigate the utility of frozen section of uterine curetting in ruling out the possibility of EP, 715 cases of uterine curetting from July 1999 to May 2009 were reviewed and compared histopathologically, especially those cases between frozen sections and paraffin sections.

Materials and Methods

The study included 715 cases of uterine curetting from July 1999 to May 2009 that were selected retrospectively. All the patients were administrated by a complete endometrial curettage. The selection criteria included cases in which the frozen and paraffin sections were simultaneously performed due to the clinical diagnosis ruling out EP. Two cases were excluded because no paraffin sections were performed.

Procedures of sampling, preparing and interpreting the curettings:

1) For the diagnosis of frozen section: usually only one block of section was frozen for diagnosis. If intrauterine pregnancy was suspected in the frozen section, one more block was sampled for the diagnosis of frozen section.

2) For the diagnosis of paraffin section: the frozen tissues were also fixed, embedded, and routinely prepared for diagnosis. One block was selected for paraffin section if the evidence of intrauterine pregnancy had appeared in the frozen sections. The remaining fragments were sectioned to avoid overlooking the tissues of intrauterine pregnancy if no evidence of intrauterine pregnancy had appeared in the frozen sections. The diagnosis of paraffin section was based on a thorough microscopic examination of the fixed frozen tissues, the original frozen section, and the paraffin sections. (Occasionally, the diagnosis of re-embedded frozen tissues is not the same as that of the original frozen section because tissues in the original ones may be cut away and lost forever).

The diagnoses of paraffin section and frozen section were concordant if either of the following interpretations were made:

1) The diagnosis of the paraffin section and that of frozen section were the same.

2) Frozen section diagnosis was trophoblast cells or basal deciduas; paraffin section diagnosis was villi.

3) Frozen section diagnosis was villi; paraffin section diagnosis was trophoblast cells or basal decidua.

The diagnoses of paraffin section and frozen section were discordant or inconsistent if either of the following reports were made:

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1) Under-diagnosed cases: frozen section diagnosis was decidua or secretory endometrium; Paraffin section diagnosis was trophoblast cells or decidua or villi.

2) Over-diagnosed cases: frozen section diagnosis was villi, basal deciduas or trophoblast cells; not any of these two tissues had appeared in the paraffin section. Review of those frozen sections and paraffin sections denied any of these three issues by experienced hands.

Inconsistent sections were reviewed by two pathologists to analyze the reasons for its inconsistency and follow-up data was obtained if necessary. For three cases of frozen sections, the pregnancy tissues could be seen, but the paraffin sections did not show the evidence. The original diagnoses were proved correctly after review and the follow-up data suggested the intrauterine pregnancy. Therefore, the diagnoses between frozen section and paraffin section were believed to be concordant.

Results

1. Clinical data

Patient age ranged from 19 to 48 years (mean 30.6), with amenorrhea period from 30 to 70 days (mean 50.2). Of all 402 cases of intrauterine pregnancy made based on frozen section, 401 cases were concordant with the diagnosis on paraffin section and one case was over-diagnosed in frozen section. Of all 313 cases with evidence of pregnancy, 281 cases were concordant and 32 cases under-diagnosed.

For the patients whose diagnoses were discordant between frozen section and paraffin section, their age ranged from 19-44 years (mean 31.0) and amenorrhea period was 39-62 days (mean 48.9). A total of 32 cases of frozen sections were under-diagnosed, of which 22 cases of frozen sections were interpreted as decidua only, ten cases of frozen sections were interpreted as secretory endometrium. Of 22 decidua-only cases, six cases had deciduas basalis in paraffin sections. Of ten secretory endometrium cases, eight cases of paraffin sections had villi and two cases of paraffin sections had deciduas basalis. For one case with over-diagnosed of frozen section, the interpretation was deciduas basalis in frozen section and only deciduas was seen in paraffin sections. Reviewing this frozen section, the authors believe there was no pregnancy evidence appearing on the slide.

2. Ending of patients without intrauterine pregnancy in frozen section diagnosis.

There were 313 patients without intrauterine pregnancy in frozen section diagnosis, such as trophoblast cells, basal decidua or villi, of which 32 cases had intrauterine pregnancy evidence in paraffin sections and 281 cases had no intrauterine pregnancy evidence in paraffin sections. In 281 cases, 259 cases were proved with extrauterine pregnancy after abdominal laparotomy. For 22 cases, their serial serum β -HCG titer quickly reduced to normal after curettage and the B-ultrasonic results showed that "there was no intra or extrauterine gestational sac".

3. Ending of patients with intrauterine pregnancy evidence in frozen section diagnosis.

1) There was a total of 402 patients with intrauterine pregnancy evidence in frozen sections. For one case, villi were seen in both frozen section and paraffin section, β -HCG titer continued to rise, and the B-ultrasonic results showed that "there was a hemorrhagic ovarian mass beside left adnexa". Therefore the patient was diagnosed with a "heterotopic pregnancy". The patient was administrated with methotrexate, and discharged with normal serum β -HCG level.

2) There were 72 cases with deciduas basalis or trophoblast cells in frozen section, of which 47 cases of paraffin sections had villi, 21 cases of paraffin sections had basal deciduas only, and three cases of paraffin sections had deciduas tissue or secretory endometrium. After review of the latter three cases, decidua basalis was exactly seen in frozen sections; one case of frozen section was decidua basalis and only decidual tissue was seen in paraffin sections.

4. Analysis of the reasons for under-diagnosing the frozen sections

Thirty-two cases (4.5%, 32/715) were under-diagnosed after reviewing the frozen sections, of which 18 cases (56.3%, 18/32) had no villi sampled in the frozen sections and there were intrauterine pregnancy tissues in the re-sampled paraffin sections, in which three cases (9.4%, 3/32) it could not be seen whether the intrauterine pregnancy tissues were present or not in the re-sampled paraffin sections due to poor preparation of frozen sections. Of these 32 cases, 14 cases (43.8%) of frozen sections were reviewed with intrauterine pregnancy tissues (a large number of fibrinoid deposits mixed with trophoblast cells were seen in five cases of frozen sections; small amount of decidua basalis were seen in three cases of frozen sections; Villi were seen in six cases of frozen sections, in which a two-layer trophoblast was seen in one case with significant edema and expansion, but the double layer structure was thin and interstitial structure was not clear, and re-cutting (section the block at deeper levels) or re-sample (select tissues at the remaining fragments) was required at that time. In one case of frozen sections, the villi were mixed with many secretory glands and difficult to distinguish).

5. Analysis of the reasons for over-diagnosing the frozen sections

In one case with over-diagnosed frozen section, the frozen section suggested decidua basalis and no pregnancy evidence was seen both in frozen section and paraffin section after review. The authors contacted the patient, and the urine pregnancy test was negative one week after uterine curettage, β -ultrasound showed "there was no intra and extra uterine gestational sac" with clinical diagnosis of intrauterine pregnancy. However in our study, it was considered as over-diagnosed.

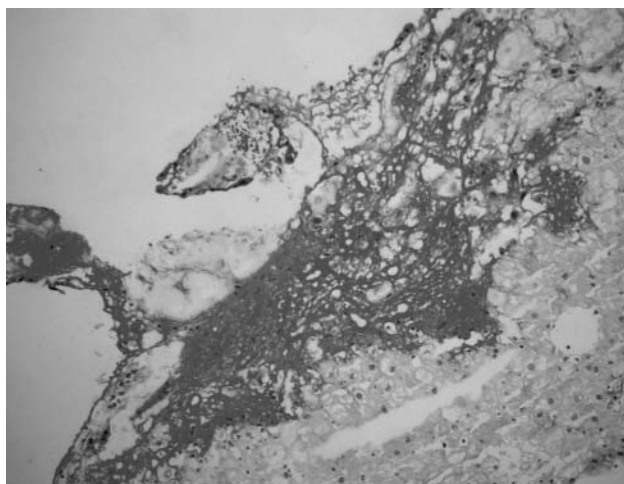


Figure 1. — Nitabuch's fibrinoid. A thick layer of eosinophilic fibrinoid deposits can be seen, with immediate trophoblast cells and free syncytiotrophoblast cells in the vicinity. (hematoxylin-eosin, original magnification $\times 100$).

6. Comparison of frozen section results and pathological results

Of 715 cases, the diagnosis of frozen sections in 682 cases (95.4%) was concordant with paraffin sections and there were 32 cases with no intrauterine pregnancy evidence seen in frozen sections but with pregnancy evidence in paraffin sections, and one case of paraffin section with decidua basalis, and no intrauterine pregnancy evidence in paraffin section.

Conclusions

Problems existed in the diagnosis of frozen sections

1) Most discordant cases (32/33, 96.7%) were patients with under-diagnosed frozen sections in this group of experiments, and the problems that were diagnosed with frozen sections were analyzed as follows:

A. Inadequate selecting of the specimen at the time of frozen section. In this study, no intrauterine pregnancy tissue was sampled in the frozen sections in 18 cases (56.3%, 18/32), and in the final diagnosis, intrauterine pregnancy tissue was seen in re-sampled sections, which suggested that the biopsy technique needed to be improved. In general, when there were no obvious villi macroscopically, the hemorrhagic areas of the curettage specimen increased the detection rate of intrauterine pregnancy tissues.

B. Poor quality of sections. Of 18 cases of frozen sections with no intrauterine pregnancy tissue drawn, three discordant cases were caused by poor quality of section preparation, and a clear section could have facilitated the reading.

C. Inexperience of the pathologist. In 32 cases of under-diagnosed frozen sections, there were 14 cases with in-

trauterine pregnancy tissues after review, so improving the experience of interpretation is necessary.

a) Nitabuch's fibrinoid (Figure 1). One layer of fibrinoid deposits on the surface of deciduas is known as Nitabuch's layer. There are trophoblast cells in the vicinity of this layer, which is the evidence of intrauterine pregnancy [5].

b) Decidua basalis. Decidua basalis is the deciduas at the site of implantation. Intermediate trophoblast cells are characteristic of dark stained cells scattered within the deciduas, the existence of decidua basalis can be regarded as intrauterine pregnancy. In this study, of under-diagnosed 32 cases, decidua basalis was seen in three cases after reviewing the frozen sections, and these three cases could be diagnosed as intrauterine pregnancy.

c) Syncytiotrophoblast cells (ST). Isolated STs, with hyperchromatic multi-nuclei, often fall from the villa. The emergence of free STs can be regarded as intrauterine pregnancy. If small amounts of free STs and villi occurred in the curetting, re-cutting or re-sampling was required to find the deciduas basalis. Because, in rare cases, a small amount of free trophoblast cells and villi can backflow into the uterine cavity through isthmus portion of the fallopian tube. In this study, after reviewing the under-diagnosed frozen sections, free trophoblast cells were seen in five cases, and the follow-up results showed intrauterine pregnancy.

d) When the following images occurred in the sections, re-cutting or resample were performed to improve the detection rate of intrauterine pregnancy:

- many open blood sinusoid and extensive areas of hemorrhage in slides;
- much fibrinoid deposits.

2) Problems existed in the over-diagnosis of frozen sections

A. In this group, one case was over-diagnosed, and the decidual tissues were misdiagnosed as decidua basalis, and after review, there was no decidua basalis, which was related to the diagnosis experiences.

B. Improving the experience of interpretation on microscopic slides.

a) Identification of villi and decidua. Sometimes in frozen section, small amount of deciduas may be encapsulated by endometrium glands, which can be confused with the villi. The outline of glandular cells is of single layer structure, and the villa is surrounded by two-layer trophoblast cells with cytotrophoblasts at the inner layer and STs at the outer layer.

b) Identification of blood vessels and highly degenerative villi in the fibrinoid deposits. Both of them have tubular structures, degenerative, and obscure figures. However the blood vessel contains erythrocytes or plasma-like amorphous materials and the villa has two-layer trophoblast cells.

c) Identification of glands with Arias-Stella (A-S) change and trophoblast cells fall from the villus. Both of them have larger dark-stained nuclear. The hyperchromatism cells with A-S change are glandular and emerge on the spongiosa

layer of endometrium. The trophoblast cells fall from the villi and are scattered in the fibrinoid deposits or on the surface of the deciduas.

3) In case of rare heterotopic pregnancy (it is reported that its incidence is about 1:30,000 and the incidence has increased with the development of assisted reproductive technology), we need to rely on other clinical and ancillary laboratory, and the frozen section and only pathology can diagnose the tested scrapings and cannot predict whether or not the extrauterine pregnancy is incorporated at the same time.

7. Significance of the scrapings in the diagnosis of frozen sections on excluding the extrauterine pregnancy.

There were a total of 715 cases in this study, of which frozen section diagnosis were discordant with paraffin section diagnosis in 33 cases and most of them were under-diagnosed, and one case was over-diagnosed, which was related to the diagnosis experiences. Previously reported data have shown that using frozen section to diagnose intrauterine pregnancy has a certain false negative and small amount false positive. Spandorfer *et al.* reported a sensitivity of 78.3%, specificity of 98.4% for the diagnosis of frozen section [1]; Barnhart *et al.* reported sensitivity of 87.5%, specificity 100% [2]; Barak *et al.* 76%, 97.8%, respectively) [3]. In the present study, there were a total of 715 cases in a decade with sensitivity of 92.6%, specificity of 99.6%, positive predictive value of 99.7%, negative predictive value of 89.8%, and frozen section accuracy rate of 95.4%, so the authors believe that the diagnosis of frozen sections are valuable for excluding the extrauterine pregnancy. The diagnosis of frozen sections can determine whether the curetting contain the evidence of intrauterine

pregnancy in a short time (20-30 min), thereby the patients with exact intrauterine pregnancy can avoid being hospitalized for observation and go home without misgivings; the patients with highly suspected extrauterine pregnancy can be immediately confirmed with further treatment, the waiting time is reduced, the waste of medical resources is also reduced, and the diseases of the patient also can be effectively and quickly treated.

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