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CASE REPORT

Embryoscopy and its place in gynaecology: a case series and review of literature

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ABSTRACT

Background. The missed abortion has always challenged clinicians and researchers to investigate the underlying cause. In the last few decades, embryoscopy has become an indispensable tool in the field of gynaecology and related reproductive disorders. The current study aims to explore the application and intervention of embryoscopy in cases of missed abortion and attempt to understand the cases of missed abortion.

Case presentation. Presenting a series of two cases of missed abortion. The patients were counselled for embryoscopy. During embryoscopy, the products were removed and sent for the analysis of chromosomal abnormality using fluorescence in situ hybridisation technique. Further, a non-systematic review was conducted by collecting various articles on the techniques of embryoscopy, fetoscopy and fluorescence in situ hybridisation technique. The cases of missed abortion were also included in the research. The articles were collected from PubMed, Scopus, Cochrane, Medline, Embase, Web of Science, *etc*.

While examining, the gestational sac and embryo were found to be attached to the uterine wall, but the embryo node was not observed during embryoscopy. Additionally, chromosomal aberrations using fluorescence in situ hybridisation technique were also found to be negative.

Conclusions. There were no morphological changes found in the uterine cavity, including the conceptus. Furthermore, there were no chromosomal aberrations observed in the embryo, suggesting the presence of underlying genetic lesions that are not detected by fluorescence in situ hybridization. More studies into genetic and morphological changes utilising the latest and

advanced techniques are required for the understanding of factors involved in the missed abortion cases.

Key words

Embryoscopy; fetoscopy; malformations; prenatal conditions; gynaecological conditions.

INTRODUCTION

The direct visualization for fetal and prenatal diagnosis of abnormalities by using a scope has been applied in the past. One of the earliest hysteroscopic transuterine visualizations was performed for fetuses in the 2nd trimester [1]. The pregnant women were given both local as well as general anaesthesia. Since the earliest use of scope in the diagnosis of fetuses in 1954, the technological advancements in the field of visualization techniques of embryo development have come a long way. Embryoscopy involves the application of endoscope using fiber optics technology that is introduced through either abdomen or cervical canal. The scope reaches into extracoelomic space, where the developing embryo is directly visualised through intact amnion membrane. It is typically performed between 5 weeks to 11 weeks of gestation. Since chorion fuses with amnion after 11 weeks, the visualization using embryoscopy becomes impossible. Although, diameter of the endoscope ranges between 1.7 mm to 3.5 mm with varying lens angle from 0 - 30°, it is passed through the cervical canal or abdomen under the ultrasound guidance [2]. To insert the endoscope into extracoelomic space, a rapid thrust is applied to penetrate the chorionic membranes. Once the endoscope is introduced into the extracoelomic space, it is possible to examine phenotype of the embryo, including face, head, umbilical cord, dorsal and ventral wall and yolk sac.

Nevertheless, the embryoscopy technique remains invasive in nature with risk to pregnant women and the fetus. The application of embryoscopy and fetoscopy evolved as a common technique to visualize the developing fetus for the diagnosis and therapeutic purposes in the 1970s. In one of the earliest reports, fetoscopy was used to visualise the malformations, including neural tube defect in the fetus [3, 4]. However, the diagnostic application of embryoscopy was largely abandoned, after the advent of ultrasound. Later in the 1990s, the miniaturized and light instrument with video embryoscopy became prevalent for therapeutic procedures in the uterine cavity of pregnant women [5, 6]. Although prenatal screening were used to detect the abnormalities in the fetuses, the treatment could only be performed after the birth. In some conditions, without prenatal interventions, organ damage or intrauterine fetal death (IUFD) was also possible. In such cases, open fetal surgery may lead to premature delivery and preterm premature rupture of membrane (PPROM). Fetoscopy, due to its minimal invasiveness, has huge potential to provide therapeutic alternatives [7]. The cases for fetal interventions with embryoscopy remain rare due to high risk of medicolegal risks. An initiative was taken by the European Union in 1998 by bringing medical experts and endoscope manufacturers, which led to development of multiple purposefully designed endoscopes based on highly specific fetal conditions. One of the first applications of such condition specific fetoscopes was complicated monochorionic multiple pregnancies. Moreover, various conditions were defined, which were specific for the application of embryoscopic intervention [8]. In recent times, application of embryoscopy only for the diagnosis has become rare.

Hysteroscopic uterine evacuation of early pregnancy loss using tissue removal devices seems to be safe and feasible, it helps in accurate localisation of gestational sac in the uterine cavity.On the other hand embryoscopy can be done before uterine evacuation and this technique is more accurate and for foetal chromosome karyotyping with lower maternal cell contamination.

The application of embryoscopy has demonstrated several advantages over Dilitation and currettage (D&C). Embryoscopy allows the precise localization of the gestational sac inside the uterine cavity, I ower maternal cell contamination so that result can be more accurate than D & C for fetal chromosome karyotyping. Embryoscopy is under vision procedure, which may reduce retained products of conception rate and risk of intrauterine adhesion formation. Direct vision of morphological alteration of embryos also provides significant information for genetic counselling. However its limitations is around 11 weeks when the chorion and amnion fuse and there is risk of rupturing the amniotic membrane.

Aim and objective

- To explore the application and intervention of embryoscopy in gynaecological conditions, especially in the cases of missed abortions.
- To understand the cause of missed abortions.

CASE PRESENTATION

The missed abortion of 2 patients were diagnosed at the department of gynaecology, PSRI Hospital, New Delhi. As it is a case series - its limitation is small sample size but it provides detailed and quality information about the outcome of the study.

Case 1: The patient had a history of 3 abortions in the past (P0L0A3). The patient was presented with USG suggestive of missed abortion. The blood sample of the patient was sent for relevant investigations. The patient was counselled for embryoscopy. Based on the vaginal examination, uterus was found to be 6-8 weeks size, anteverted, and bilateral fornices free. The product collected from embryscopy was sent for histopathological analysis by fluorescence in situ hybridization for aneuploidy. The fluorescence in situ hybridisation technique analysis was performed on 200 interphase nuclei.

Case 2: The patient had a history of missed abortion (P0L0A1). The patient was presented with spotting per vaginal since day 1. The blood sample of the patient was sent for relevant investigations. The patient was counselled for embryoscopy based on vaginal examination. The uterus was found to be 6 weeks size, anteverted, and bilateral fornices free. The product collected from embryoscopy was sent for histopathological investigations and fluorescence in situ hybridisation technique analysis for aneuploidy. The fluorescence in situ hybridisation technique was performed on 200 interphase nuclei.

Literature survey: Various articles were assessed for the non-systematic review on the place of embryo-fetoscopy in the field of gynaecology, including methods and clinical applications of the embryoscopy and fetoscopy in context with the interventions and diagnosis of missed abortion cases. The literature assessed also helps to confirm and clarify knowledge of embryonic development and disorders associated and to provide early prenatal diagnosis of genetic

disorders (this ranges from 7%to 18%).The articles were reviewed by searching various databases, including PubMed, Google Scholar, Embase, Web of Science, Science Direct, Cochrane database etc.

The articles were filtered based on full text availability, year of publication and relevance of the topics. The studies with description of embryoscopy and fetoscopy, including their application and interventions in the certain conditions were selected for the review. The keywords used were embryoscopy, fetoscopy, embryo-fetoscopy in diagnosis and their interventions in context with gynecological and prenatal conditions.

Case 1: Upon embryoscopy, gestational sac was observed on the posterior uterine wall. Yolk sac was found intact, but the embryo node was not visualized. The biopsy was collected and the rest of the product was removed during the procedure. The aneuploidy detection for POC using fluorescence in situ hybridisation technique was found to be negative (Fig 1 A & B).

Case2: It was found that the embryo and sac were attached to the fundus and posterior wall in front of the right ostia. No apparent abnormality was visualized during embryoscopy. Moreover, rest of the uterine cavity, left ostia, and cervical canal were observed to be normal. The biopsy was collected and rest of the product was removed during the embryoscopy. The fluorescence in situ hybridisation result showed two signals pertaining to a normal sex chromosome 13, 18, 21 and normal sex chromosome pattern in the cells. The aneuploidy detection of POC (products of conception) using fluorescence in situ hybridisation was found to be negative. The histopathological examination showed chorionic villi, trophoblastic cells, and secretory endometrium with markedly decidualized stroma (Fig 1 C & D).

DISCUSSION

In this case study, we investigated embryonic products in two patients with missed abortion, using embryoscopy. We found embryo and sac attached to the posterior wall of the uterine cavity in both the cases. During the examination, there was no synechia, intrauterine septum or polyp (fig 1). Beyond the uterine cavity, it was revealed that both ostia and cervical canal appeared normal . Although, certain abnormalities and morphological changes in the cases of missed abortion remain undetected by ultrasound which were observed by embryoscopy [9], leading to expansion of diagnostic tools used for evaluation of pregnancy loss. According to a study, the correlation between transvaginal hysteroscopy and ultrasound for the assessment of intracavitary uterine pathologies in 105 women with asymptomatic postmenopausal endometrial thickening was found to be insignificant [10]. Nevertheless, Palmero et al considered embryoscopy to be the gold standard for diagnostic exams in gynecological interventions [10]. Moreover, another study reported an established correlation between embryoscopy and histopathology, in the context of morphological changes in the inflammatory state of endometrium [11]. Embryoscopy could be useful in the study of highly characterized cohort subjects with missed abortions with no apparent chromosomal abnormalities in the product. During the pregnancy period, the development of fetus is a sequence of events that allows the formation of various organs and body parts in a specified period of time (Table 1).

With the help of embryoscopy, direct visualization of uterine cavity, gestational sac, and embryo per week is possible based on the above findings. Embryoscopy also helps in prenatal diagnosis of chromosomal abnormalities as well as recognisable external fetal abnormalities.

Additionally, it also provides accurate information of fetal development, which allows to minimise the risk of miscarriage with the help of both genetical and morphological information of the embryo.

Typically, fluorescence in situ hybridisation technique is applied to detect common chromosomal aberrations related to trisomies of the autosomes 13, 18, or 21 (Down syndrome). Double trisomy or aneuploidy, which is a result of gain or loss of at least two chromosomes, is observed in 0.21 – 0.28% of the aborted fetuses. Disorders related to sex development are indicated by the aberrant number of genosomes, X and Y. Severe developmental and metabolic disorders have been associated with diseases, such as Ulrich-Turner-Syndrome (45, X) or Triple X Syndrome (47, XXX). The prevalence of chromosomal abnormalities detectable in the newborn including chromosomes, 13, 18, 21, X and Y has been found to be 0.92% [12]. In the current study, we found that the fluorescence in situ hybridisation technique analysis performed on 200 interphase nuclei showed two signals pertaining to a normal number of chromosomes 13, 18, 21 and normal sex chromosomes patterns in these cells, which suggest no chromosomal abnormalities in the conceptus. The development of embryo consists of precisely programmed developmental events, which involves multiple genes to be regulated in synchronized fashion for the growth and morphogenesis. It has been documented that the abnormal development observed by embryoscopy in the cases with normal chromosome were as severe and gross as the cases with abnormal chromosomal abnormalities [13], which might suggest the presence of genetic lesion that are undetectable by fluorescence in situ hybridisation technique. However, more studies are required in this field to determine the reasons for the missed abortion cases, where chromosomes are found to be normal in the product.

CONCLUSIONS

While examining, the morphological structure of the uterine cavity, including embryo and sac attachment, intrauterine septum, polyp, synechia, lest ostia and cervical canal, appeared normal. Moreover, there were no apparent chromosomal abnormalities observed in the cases with missed abortion, which might suggest underlying genetic lesions, which remain undetectable by the fluorescence in situ hybridization technique. Also in the above two cases, after the morphological and genetic study, patients were counselled well and reassured. They were counselled to conceive again and at present both patients are carrying a healthy pregnancy till date. A deeper morphological and genetic study is warranted to understand the attribution of missed abortion cases.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

R.M.: Conceptualization, Supervision, Investigation, Formal Analysis, Methodology, Patient consent, Validation. N.S., Data curation, Writing – original draft, Writing – review & editing, Investigation

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

N/A.

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Figure 1. Images taken from embryoscopy of case 1 (**A & B**) and case 2 (**C & D**) showing G-sac.

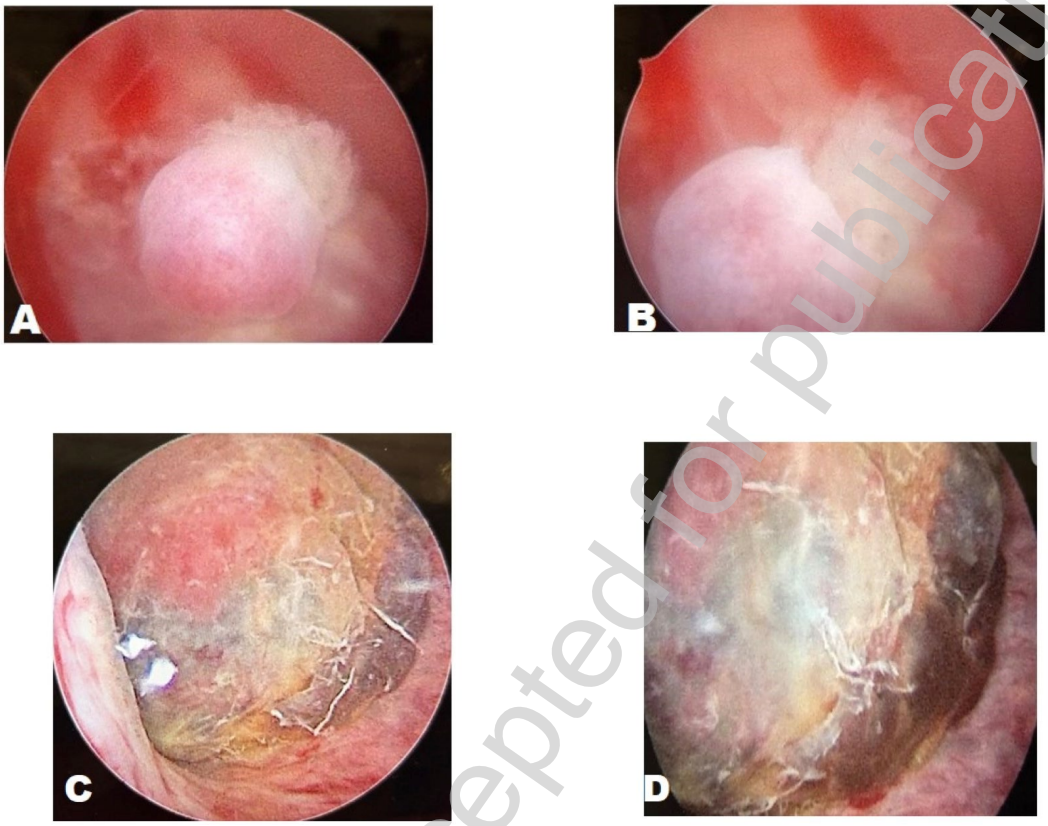

Table 1: Representation of different events of the fetal development according to the gestational periods during the pregnancy.

Gestational period	Events of fetal development
5 weeks	· G sac / yolk sac · Primitive umblical ring
6 weeks	· G sac / yolk sac / fetal pole · Formation of foot plate · Auricular hillocks · Prominent cerebral vesicels
7 weeks	· Formation of eye lid · Digital rays in footplate · Limbs · Midgut formation
8 weeks	· Fingers and toes become free and longer · Eyelid and auricle more develop
9-12 weeks	· Development of lower and upper limbs · External genitalia differentiation