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REVIEW ARTICLE

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Embryofetoscopy: a new "old" tool

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Abstract Embryoscopy is the direct visualization of the embryo between 5 and 8 weeks' gestational age. Fetoscopy is the direct visualization of the fetus after 8 weeks of gestation. Both are performed by inserting a fiber-optic scope, either transabdominally or transcervically, into the extracelomic space when the procedure is done before 11 weeks or inside the amniotic cavity when it is done after 11 weeks. Embryofetoscopy is likely to find applications in confirming and further clarifying our knowledge of embryonic development and in the prenatal investigation of high-risk pregnancies for recurrent genetic disorders. Further evolution of endoscopic instruments and embryoscopic technique could give embryofetoscopy a potential for early gene and cell therapy as well as for surgery in utero. We also present our preliminary experience using transcervical embryoscopy for direct visualization of the 1st-trimester embryo in women opting to terminate pregnancy.

Keywords Embryoscopy · Fetoscopy · Antenatal diagnosis

Introduction

The use of a scope for direct fetal visualization and prenatal diagnosis of fetal anomalies has been used in the past. A pioneer in the field was Bjorn Westin [1], who, in 1954, performed a hysteroscopic transuterine direct visualization of three fetuses prior to termination in the 2nd trimester, using a 10-mm McCarthy panendoscope. Two of the patients were given general anesthesia, whereas the third woman was given local anesthesia. In the last case, vigorous limb movements of the fetus were seen as well as swallowing more than 30 times per minute. Much later, during the 1970s, Scrimgeour and Valenti [2, 3] performed direct endoscopic examinations of fetuses via a laparotomy and incision in the myometrium. Eventually, in the 1980s, a new technique ("fetoscopy") allowed the introduction of a scope transabdominally under real-time ultrasound guidance for close examination of the fetus in utero, as well as for sampling of fetal blood, skin, and other tissue [4, 5]. However, high fetal loss rates (4–8%), as well as the evolution of high-tech ultrasound for prenatal diagnosis of fetal abnormalities with ultrasonically-guided needle fetal blood sampling [6] made fetoscopy seem outdated at the end of 1980s. Yet the recent evolution in fiber-optic technology has lead to miniaturization of endoscopic equipment and has constituted the procedure possible during the 1st trimester, thus giving it a new perspective.

Embryoscopy

This technique involves the introduction of a fiber optic endoscope either trans-abdominally or through the cervical canal, into the extracoelomic space and direct visualization of the developing embryo through an intact amnion membrane.

The procedure can be performed as early as 5 weeks of gestation and until 11 weeks, after which the fusion of the chorion with the amnion make it impossible. The endoscope, which can vary in diameter from 1.7 mm [7] to 3.5 mm and in lens angle from 0 to 30º, is passed transcervically or transabdominally under ultrasound guidance. When it reaches the chorion, a rapid thrust is applied perpendicularly to the chorionic membranes so that it will penetrate them and enter the extracelomic space. From

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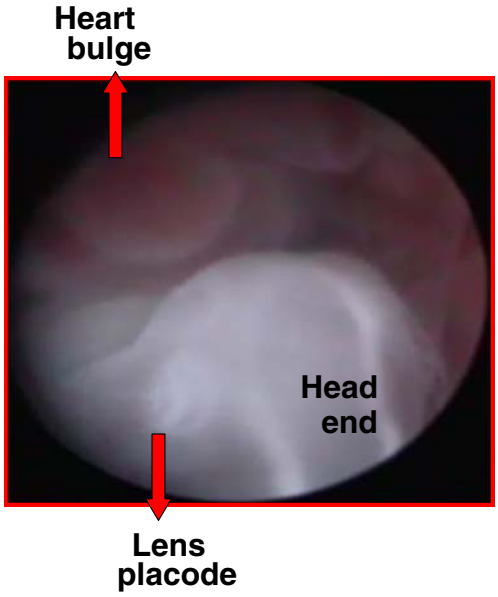

Fig. 1 Embryo (view from above) at 5 weeks

within the extracelomic cavity, a complete examination of the phenotype of the developing fetus is possible, including the head, face, dorsal and ventral walls, umbilical cord, and yolk sac.

Indications

Normal embryonic development

Much of our understanding of the mechanisms of normal and abnormal human embryonic development is based on detailed observations of aborted human embryos as well as insights gained through studies of normal and abnormal subhuman embryos. It has been long recognized that similar appearances of higher vertebrate embryos with the human one suggest underlying similar developmental mechanisms. However, technical advances have improved our ability to compare the development of humans and experimental animals. For example, the three-dimensional configuration of embryonic cells as shown by scanning electron microscopy often provides clues about their behavior (e.g., the bipolar configuration of migrating cells).

In the same mode, embryoscopy can be an indispensable tool for confirming and clarifying our knowledge of embryonic development. Important embryonic structures and developmental milestones can be visualized up close (Figs. 1, 2, 3, 4 and 5). At 5 weeks, the lens vesicles and facial prominences, the primary palate, lip, and midface, and the formation of the hand plates can be seen. At 6 weeks the formation of digital rays in the hand is noted, as well as the formation of the foot plate, the auricular hillocks, and the prominent cerebral vesicles. At 7 weeks the formation of the eye lids can be visualized, along with the digital rays in the foot plates, the nipples, limbs extending ventrally, the notches between the digital rays in the hands, and a prominent midgut herniation. At 8 weeks, fingers and toes become free and longer; the eyelids and auricles are more developed; external genitalia are still sexless; there is a distinct herniation bulge in the umbilical cord; the tail is disappearing; and the embryo shows distinct human characteristics. From 9 to 12 weeks, the further development of the upper and lower limbs occurs and they reach their final relative lengths; the intestines return to the abdomen; and the external genitalia are differentiated.

Embryoscopy in missed abortions

Because the embryos in most cases of missed abortion are damaged because of their spontaneous vaginal passage or the surgical manipulations during the instrumental evacuation of the uterus, pathologic examination of 1st-trimester embryo losses is especially difficult. Embryoscopy in missed abortions can provide invaluable information on the phenotype of the embryos and help us clarify the specific mechanisms leading to the observed developmental defects and death in utero. The causes behind these defects and death can be heterogeneous, originating from an abnormal karyotype, a single gene defect, or an accidental event. Information obtained by embryoscopy can identify the risk of recurrence in future pregnancies so that parents at high risk can be offered genetic counseling [8].

Prenatal diagnosis

High-resolution ultrasonography is the most common established approach to antenatal diagnosis of congenital

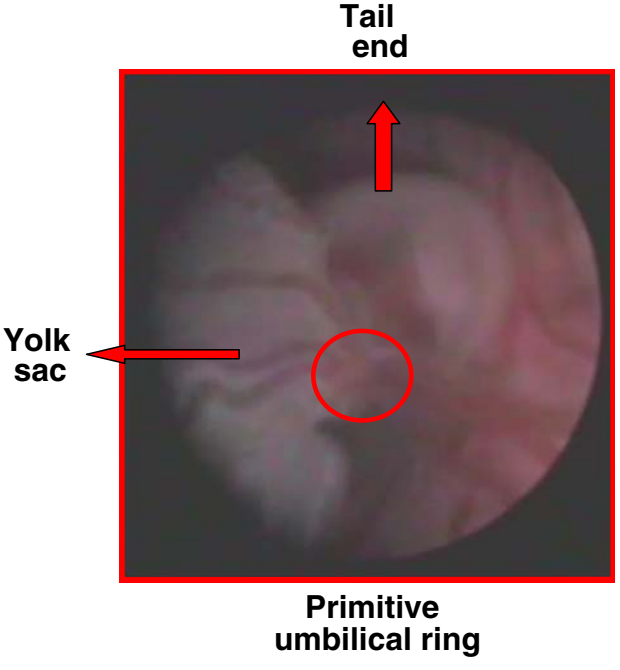

Fig. 2 Yolk sac and umbilical ring at 5 weeks

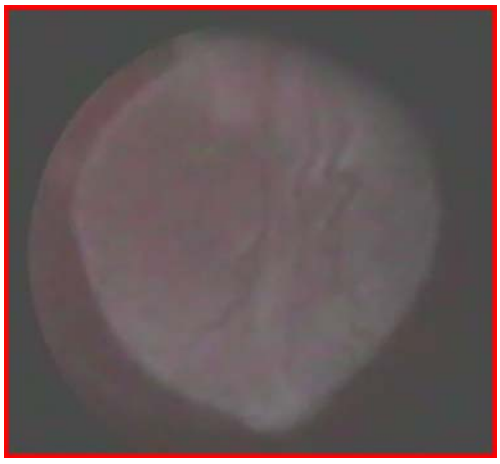

Fig. 3 Yolk sac at 5 weeks

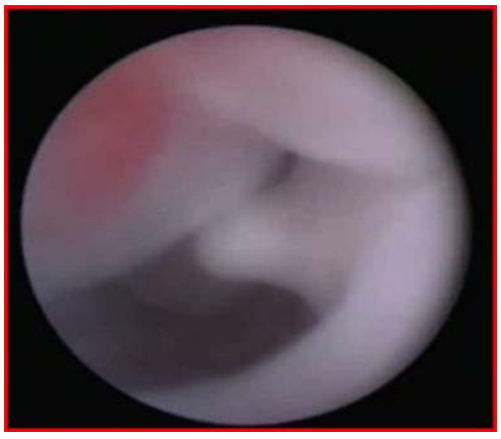

Fig. 5 Detail of phallus and labioscrotal folds at 7 weeks

abnormalities during the 1st and 2nd trimesters. But in situations where there is a high family risk of recurrence of genetic disorders that project onto the embryonic phenotype or when antenatal ultrasound screening is highly suggestive of a congenital anomaly, embryoscopy could serve as a conclusive verification tool. Dumez et al. [7] performed diagnostic embryoscopy in 42 patients at high risk for dominant autosomal genetic disorders. Six patients eventually were diagnosed as having embryos with facial or limb anomalies, and their pregnancies were terminated. Overall success in visualizing the embryo was 97%. Of the rest of the pregnancies, five (12.8%) miscarried between 11 and 23 weeks. In total, 31 normal babies were delivered and have developed normally since then.

Hobbins et al. [9] performed transabdominal fetoscopy in two cases at high risk for Smith–Lemli–Opitz syndrome. The procedures were performed at 10+4 and 11+5 weeks. The authors were able to diagnose polydactyly and confirm the syndrome in one case. The syndrome was excluded in the other case, which ended in the birth of a normal baby at 35 weeks.

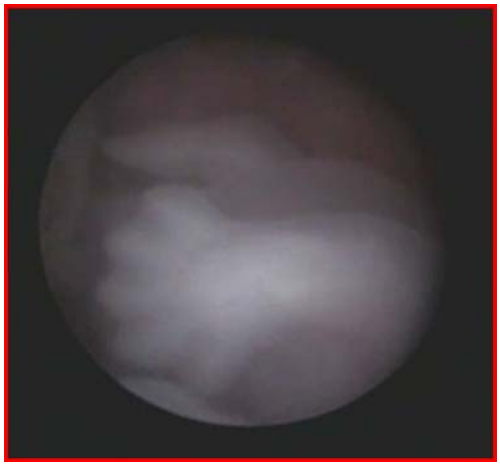

Fig. 4 Upper limb at 7 weeks

Dommergues et al. [10] diagnosed van der Woude syndrome at 11 weeks by identifying cleft lip by embryoscopy. In this autosomal-dominant condition, expressivity is variable, and DNA linkage analysis was not conclusive in diagnosing whether the embryo was affected. The pregnancy eventually was terminated. The same team was later able to diagnose Meckel–Gruber syndrome in another case by performing transcervical embryoscopy at 10+ weeks' gestation [11]. They were able to visualize feet and hand postaxial polydactyly as well as cervical encephalocele because of the irregular shape of the posterior aspect of the fetal head. The same condition was diagnosed by Quintero et al. [12] at 11 weeks' gestation by using embryoscopy to visualize postaxial polydactyly and an occipital encephalocele, although ultrasound imaging had failed to show any of the three cardinal features of Meckel–Gruber syndrome.

In a more recent series, Ville et al. [13] reported two cases in which 11-week fetuses presented with increased nuchal translucency (4 and 6 mm, respectively) and generalized edema. In both cases, chorionic villi sampling (CVS) sampling showed a normal 46xx karyotype. However, the ultrasound features of early hydrops led the parents to request further examination by embryoscopy. In the first case, transabdominal intraamniotic embryoscopy revealed facial dysmorphia with a short, flat, and upturning nose with a long filtrum. In the second case, embryoscopy revealed the association of clinodactyly and multiple, mainly frontal, angiomas. This couple had a previous history of having a child with unexplained mental retardation and a large cutaneous angioma. The parents in both cases opted for terminating the pregnancies. In another case, the same team performed transabdominal embryoscopy at 13 weeks after an ultrasound finding of micrognathia. This couple already had a child affected by Pierre Robin syndrome with severe mental retardation. Embryoscopy confirmed mandibular hypoplasia, which is associated with recurrence of Pierre Robin syndrome, and this pregnancy was also terminated.

Fetal blood sampling and therapy

Currently, CVS allows prenatal diagnosis at 9–12 weeks. There are situations, however, in which fetal blood is also needed later to clarify deviant chromosomal findings. Because fetal blood sampling cannot be performed by existing technology until the 2nd trimester, embryoscopic fetal blood sampling would shorten the wait and reduce parental anxiety. Reece et al. [14, 15] have been paving the way in this field, having been able to successfully access the embryonic-fetal circulation and obtain a small aliquot of blood in five out of eight cases (62%). They used a 3.5-mm fiber-optic endoscope passed transcervically in women undergoing pregnancy termination. Fetal blood was retrieved with a 26-g heparinized needle passed through the endoscope's side port and inserted either into the umbilical cord or the blood vessels of the chorionic plate.

Because embryoscopy can permit access to the embryonic circulatory system at a stage where the embryo is still immunologically immature and more susceptible to intervention, it is very likely that in the future this endoscopic technique could find application in early human gene and cell therapy. Apart from that, further development of embryoscopic instruments could give embryoscopy a role in fetal surgery, thus making it possible to treat fetal disorders before birth.

Preliminary experience

From 2000 to 2004 we performed 61 embryofetoscopies on women admitted to our department for termination of pregnancy.

Another 42 embryoscopies were performed in missed-abortion embryos. Detailed data on these procedures are currently being collected and analyzed and will be reported in future publications. We have adopted the transcervical approach, in the first cases under ultrasonic guidance but more recently without it. All patients sign an informed consent. During the procedure the patient is placed in lithotomy position under general anesthesia. The vulva and vagina are cleansed with an antiseptic solution, and the bladder is emptied. The cervix is grasped with a tenaculum, which also helps later during the rapid thrust to penetrate the chorion. A 30° fiber-optic endoscope of 2.9 mm is passed transcervically into the extracelomic cavity while trying to avoid the amnion and the placenta. When the chorion is reached, it is penetrated with a rapid thrust directed perpendicular to the membranes to avoid tenting and separation of the chorion from the uterine wall. The procedure is technically more difficult on an anteverted uterus. Camera and video recording equipment are connected to the scope and permit real-time on-monitor visualization during the procedure as well as image and video recording. After the embryo is examined as thoroughly as possible through an intact amnion, the scope is removed, and a standard procedure of suction curettage is carried out.

So far, we have had no uterine perforations by using the above described technique, nor have there been any infections or other evidence of maternal morbidity. Procedure-related postoperative pain and discomfort is no more than expected for evacuation of the uterus.

Discussion

Embryofetoscopy represents an exciting technique for visualizing the 1st-trimester embryo and fetus. Evolution in hysteroscopic instruments and changing trends toward 1st-trimester prenatal diagnosis have given new potentials to this "old" technique. Embryoscopy can be applied in women opting to terminate pregnancy and can prove an indispensable tool for confirming and clarifying our knowledge of embryonic development, since key embryo structures and developmental milestones can be visualized closely. Apart from that, in continuing pregnancies that are at high risk for recurrence of specific genetic disorders, very early prenatal diagnosis is invaluable, as parents will be given the option of early termination. Embryofetoscopy can additionally permit access to the embryonic circulatory system for early fetal blood sampling. Still, embryofetoscopy is an invasive procedure, and parents will have to counterbalance the advantage of early prenatal diagnosis against the risk of inducing miscarriage in a normal pregnancy. Embryofetoscopy in missed abortions is free of this risk and could provide us with information on the causes responsible for the failed embryonic developmental steps so that parents can be effectively counseled about future pregnancies.

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