Embryological Background for Fetal Surgery

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Congenital malformations are one of the main topics, which must be addressed in the 21st century. Fetal surgery is expected to become a routine procedure for malformed fetal patients in the near future. This paper presents some important aspects of the embryological background required for fetal surgery and shows normal human embryos between the 4th and the 8th week of development.

Key Words: Fetal surgery, human embryo, Carnegie stage

Congenital malformations are gross structural abnormalities, which are attributed to abnormal development and which are present at birth. Congenital malformations currently account for 3% of all live births, and a further 3% is added during the first year after birth. They are one of the main topics to be addressed in the 21st century.

Until recently, when a fetus was diagnosed with a congenital malformation the expectant parents had three options—the termination of the pregnancy, waiting until term or early delivery. With the recent development of diagnostic imaging, anesthetic and surgical techniques, and the results from intensive animal studies, fetal surgery has been performed in some lethal conditions.

The rationale for fetal surgery is that early surgery can prevent progressive injury from an ongoing pathophysiology or from secondary damage associated with the intrauterine environment. However, fetal surgery is still in its infancy and currently includes only simple procedures compared to those used in adults. Nevertheless, fetal surgery is expected to become a routine procedure for the malformed fetal patients in the near future. In order to understand and treat the fetus properly knowledge of normal development is prerequisite. In this paper, some important aspects of the embryological background of fetal surgery are discussed.

ETIOLOGY OF CONGENITAL MALFORMATIONS AND ITS POSSIBLE TREATMENTS

The etiology of congenital malformations is not known clearly in most cases, but genetic and environmental factors are believed to be responsible for about 25 and 10% of congenital malformations, respectively. The remainder appear to be multifactorial in nature, that is, they are probably caused by interactions between genetic and environmental factors.

Genetic factors can be classified as numerical and structural chromosomal abnormalities and mutant genes. With the recent completion of human genome sequencing, it has become possible to treat malformations caused by genetic factors through so-called gene therapy. Gene mapping will be very helpful for the prenatal treatment of genetic diseases, but only shows a blueprint of the original human body. This map may be used as a standard for the analysis of abnormal developments by environmental factors and the resulting congenital malformations.

Among congenital malformations, other than those attributed to genetic factors, only a few life-threatening malformations are currently suitable for in utero repair, such as, urinary tract obstruction, congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, sacrococcygeal teratoma, twin-twin transfusion syndrome, and...
aqueductal stenosis.

EMBRYOLOGICAL ASPECTS OF FETAL SURGERY

Due to the size of the fetus, and the fragility of its tissues, it is almost impossible to operate upon the fetus before 18 weeks of gestation. Moreover, the risk of premature labor induced by manipulation increases greatly after 30 weeks of gestation. Therefore, most fetal operations are performed between 18 and 30 weeks.

Excepting this time limitation, fetal tissues are favorable for operation due to scarless wound healing. According to recent clinical and experimental evidence, fetal response to injury differs greatly different from that of the adult. First, acute inflammation is virtually absent in the fetus, which is attributed to the immaturity of the fetal immune system. This immunologic tolerance provides the opportunity of applying hemopoietic stem cell transplantation. Wound healing in the fetus is a rapid process without scar formation.

Extracellular matrix in the wound region is rich in hyaluronic acid and the organization of collagen in the wound shows a normal pattern.

Scarless wound healing encourages surgeons to apply fetal surgery for nonlethal malformations such as cleft lip, craniosynostosis, etc.

EXTERNAL MORPHOLOGY OF HUMAN EMBRYO BY CARNEGIE STAGE

Prenatal development can be divided into the embryonic and the fetal period. Although the fetal surgery is performed during fetal period, most of the congenital malformations are due to abnormal development during the embryonic period, which is defined as between developmental weeks 3 and 8. During this period, three germ layers are organized and the primordia of many tissues and organs are formed, and basic body plan is laid down. Over 90% of about 4,500 structures named in adult begin to develop during this period, and therefore, this is time of organogenesis. Growth is rapid and the relationship between the placenta and mother is established. The human-like face forms, and the extremities are well developed with fingers and toes. The tail is regressed, but organs are in general nonfunctional.

At present, the embryo is not within the scope of fetal surgery. But, to understand the developmental progress and to treat congenital malformations, a knowledge of embryonic morphology is vital. In addition, such knowledge is helpful for the early diagnosis of malformations.

The embryonic period can be divided into 23 stages in the human, staging system for human embryos that is now widely used. The following represents a summary of the characteristic features of the developing human embryo between 4 and 8 developmental weeks.

The 4th week

The 4-week embryo includes stages 10-13. The flat embryonic disc becomes cylindrical and the primordia of many structures begin to appear.

The stage 10 (days 22 ± 1) embryo is almost straight and has 4-12 pairs of somites (Fig. 1A). The crown rump length (CR) is 2.0-3.5 mm, and bilateral neural folds are fused at the mid-dorsal region to form the neural tube, though at this stage it remains open to the exterior via rostral and caudal neuropores. The first pharyngeal arch is formed at the future head.

The embryo of stage 11 (days 24 ± 1) has 13-20 pairs of somites and the CR is 2.5-4.5 mm (Fig. 1B). With the formation of head and tail folds, the embryonic body becomes slightly curved. The rostral neuropore is closed and the cardiac prominence is evident in the future thorax. Two pairs of pharyngeal arches are present, the first of which surrounds the stomatodeum. With the formation of pharyngeal arches, the pharyngeal pouches are formed in the inner pharyngeal wall while branchial grooves are formed at the external surface. The optic vesicle is formed by dilatation of the forebrain, and the otic placode is depressed to form the otic pit.

The stage 12 (days 26 ± 1) embryo has 21-29 pairs of somites (Fig. 1C). The CR is 3-5 mm, and with the formation of the longitudinal fold, the embryo contour has become C-shape. The caudal neuropore has now closed and 3-4 pairs of pharyngeal arches are discernible. The upper limb
buds appear as small elevations on the anterolateral body wall at the level of 8-10 somites. The otic pit has deepened to form the otic vesicle, and the connection between the primitive gut and the yolk sac has constricted to form a yolk stalk.

The embryo of stage 13 (day 26) has over 30 pairs of somites and the CR is 4-6 mm (Fig. 1D). At this stage, the lower limb buds appear at the lumbar and upper sacral levels. Of the 4 pairs of pharyngeal arches the first 2 are more prominent and the third and fourth lie in the depression known as the cervical sinus.

**The 5th week**

The 5-week includes stages 14-15. Morphological changes are less prominent than during the fourth week, and the growth of the cephalic portion of the embryo is prominent.

At stage 14 (day 32), the CR has reached 5-7 mm (Fig. 2A), and the cervical sinus, just caudal to the second arch is prominent (Fig. 2B). The height and width of the upper limbs are nearly same, and the lens pit is evident in the head.

At stage 15 (day 33), the CR has reached 7-9 mm (Fig. 2C). The upper limb resembles a paddle shaped hand plate, and the lens pit has closed to form a lens vesicle (Fig. 2D). Nasal pit is well observed at the lateral surface.

**The 6th week**

This 6-week includes stages 16-17. At stage 16 (day 37), the CR has reached 8-11 mm (Fig. 3A). The nasal pit is directed ventrally, and the retinal pigment is observed externally. The cervical sinus is less prominent than during stage 15. Auricular hillocks have developed in the second arch (Fig. 3B), and the lower limb has a foot plate.

At stage 17 (day 41), the CR has reached 11-14 mm (Fig. 3C). The nasofrontal groove is discernible and all six auricular hillocks are evident (Fig. 3D). The cervical sinus is observed as a small pit. Distinct finger rays are developed in the hand.

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**Fig. 1.** External morphology of 4-week human embryos. (A) Stage 10, (B) Stage 11, (C) Stage 12, (D) Stage 13.
Fig. 2. External morphology of 5-week human embryos. (A) Stage 14, (B) Head and neck region of the stage 14 embryo, (C) Stage 15, (D) Head and neck region of the stage 15 embryo.

Fig. 3. External morphology of 6-week human embryos. (A) Stage 16, (B) Head and neck region of the stage 16 embryo, (C) Stage 17, (D) Head and neck region of the stage 17 embryo.
Fig. 4. External morphology of 7 week human embryos. A. Stage 18, B. Stage 19.

Fig. 5. External morphology of 8 week human embryos. A. Stage 20, B. Stage 21, C. Stage 22, D. Stage 23.
plate, and the midgut begins to herniate into the umbilical cord and is evident from external observations.

The 7th week

This 7-week includes stages 18-19. At stage 18 (day 44), the CR has reached 13-17 mm (Fig. 4A). The elbow and the fingers are discernible and eyelid folds and external ears are observed.

At stage 19 (day 47½), the CR has reached 16-18 mm (Fig. 4B). At this stage toe rays are evident, but without interdigital notches. Except this, the external changes are not as useful for staging, and the development of several internal structures, such as the cornea, the optic nerve, cochlear duct, hypophysis, vomeronasal organ, submandibular gland, metanephros and humerus are used to determine stage.

The 8th week

The 8-week includes stages 20-23. The CR has reached 18-20 mm at stage 20 (day 50½) (Fig. 5A), 22-24 mm at stage 21 (day 52) (Fig. 5B), 23-28 mm at stage 22 (day 54) (Fig. 5C) and 27-31 mm at stage 23 (day 56½) (Fig. 5D). During these stages, the upper limbs become elongated and fingers evident. Toes and knees are discernible in the lower limbs.

Head is round, disproportionally large and occupies about half of the embryonic length. Eyelids are evident and cover the eyeball to fuse in the 9-week fetus. External genitalia are also evident, but at this stage, it is impossible to distinguish between male and female by external observations only. Intestinal loops are still herniated in the umbilical cord. The transition from embryo to fetus is characterized by formation of bone marrow in the humerus and the closure of the secondary palate. From 9 week, the developing human is referred to as a fetus.

REFERENCES