Origin, formation mechanism and prenatal diagnosis of the intracranial Fetus-in-fetu. Review of the literature

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Fetus-in-fetu (FIF) is an extremely rare congenital condition, in which a fetus-like structure is found in the body of its twin. Its embryopathogenesis has not yet been established. Many investigators believe FIF represents a highly organized teratoma. More recently, the FIF has been defined as any structure in which the fetal-form is in a very high development of organogenesis with the presence of a vertebral axis. In literature less than 200 cases have been reported, mostly intra-abdominal and only 17 have been found intra-cranially. The prenatal ultrasonographic diagnosis of intracranial FIF has been suspected in 8 cases, but only one has been correctly diagnosed because a heartbeat that was of different rate to its host twin was found in the fetal-form mass.

KEY WORDS: Fetus-in-fetu - Teratoma - Twinning - Sonographic prenatal diagnosis.

Introduction

Since the first account of Fetus-in-fetu (FIF) by Meckel in the nineteenth century, approximately only 200 cases have been reported in the English literature. The FIF is a rare anomaly characterized by the presence of a fetiform mass in the body of a host twin, sometimes detected prenatally. The morphological diversity of FIF with various degrees of differentiation and multiple localizations has impeded the determination of their etiology, which continues to be obscure and controversial. Many theories have been proposed and probably there is not one that can explain the various pathological forms. In particular, the location of the intracranial FIF could have a different etiology from that of the other forms, especially those of the intraabdominal. In reviewing the currently available literature, we have focused on the rare intracranial appearances. We shall comment, in particular, on a short report which we have published, a unique account of a FIF correctly diagnosed prenatally because of evidence of intrinsic cardiac activity within it.
Discussion

The description of the birth of the goddess Athena in Greek mythology suggests that probably the ancient Greeks had knowledge of FIF. Having seduced and impregnated the goddess Metis, and fearful that her child would usurp his throne, Zeus turns Metis into a cicada and eats her whole thinking thus to terminate the pregnancy. However, Metis continues the pregnancy now located in the skull of Zeus. She becomes an integral part of him like a matrioska. During this time Zeus is plagued by terrible headaches. He finds relief only when Hephaesius strikes him on the skull and Athena emerges from the wound as a adult (Figure 1).

In ancient literature the Fetus-in-fetu was described as “congenital ventral gestation” or “a repetition of the process by which Eve was born of Adam”. One even finds “those strange instances in which a man may be pregnant with his sister” (1) or “an attempted formation of a new human being” (2). In more recent times this very rare clinical entity was made known in newspapers and magazines raising disturbing reactions in readers. So much so that Rogers in 1877 wrote, “Something marvelous; a man becomes impregnated and having no uterus uses his bladder as a receptacle. It seems that he kept not only the fetus there, but enjoyed it as a sort of companion” (3). More than a century later, in 1989, the writer King (4) published a horror novel titled “The Dark Half” in which the main character discovers that he has an unborn twin whom he absorbed during pregnancy, a form of cannibalism in utero. The twin was removed from his head when he was still a child. The neurosurgeon who performed the surgery found anatomical parts: teeth, nostril and eye.

The Fetus-in-fetu (FIF) was noted for the first time by Young (5) in 1809 and later described by Meckel the Younger, a pioneer in the science of teratology. But not until 1935 was it properly defined as the result of an anomaly in the process of twinning. Willis (6) to whom we credit this definition called it a rare entity characterized by a twin (parasite) that is included within the body of a host twin (autosite). What distinguishes the FIF from a teratoma is the presence in the included twin of an axial skeleton with a spinal cord. Frequently this skeleton together with other organs or sketches of the legs demonstrates that the parasite fetus had developed beyond the embryological stage of the primitive streak after gastrulation (12-15 days of pregnancy) with a further development of the notochord, the precursor of the spine.

Another definition proposed by Gonzales-Crussi (7) is: “Fetus-in-fetu is applied to any structure in which the fetal form is in a very high development of organogenesis and to the presence of vertebral axis”.

The definition proposed by Willis has been considered too strict because of the difficulty in many other cases in finding vertebral structures. Prominently present, instead, is a well organized fetiform mass (8-10). The lack of visualization of the spinal column does not rule out the possibility of its presence at an earlier stage. Another possibility for the lack of visualization of the spinal column may be insufficient calcification or dysplastic underdevelopment (11). Spencer (12) in 2001 proposed a more articulate definition stating that the included fetiform mass must have one or more of the following characteristics:

- a) enclosed within a distinct sac;
- b) partially or completely covered by normal skin;
- c) having grossly recognizable anatomic parts;
- d) attached to the autosite by a pedicle containing blood vessels.

The true incidence of the FIF is unknown although it has been estimated to be 1 in 500,000 births (13). In the English literature, as we mentioned above, there are about 200 cases, especially in young patients.

A suspected diagnosis is made definitive only at autopsy or after surgery.

In recent years, with more sophisticated methods (X-ray, Ultrasound, CT and MRI), the diagnosis has been easier and more accurate, especially in the prenatal period.

The location of the FIF is more common in the retroperitoneal upper abdomen, but has also been found in the mesentery, adrenal gland, pelvis, sacrococcygeal region, inguinal region, testis, liver, mediastinum, lung, oropharynx, neck and skull. In addition to the spine, there may be present in the FIF, with varying degrees of

Figure 1 - The birth of the goddess Athena.
differentiation, limbs, nervous system, genitourinary and gastrointestinal tracts, adrenal glands, spleen, liver, lung, thymus, thyroid, lymph nodes and bone tissue (14, 15).

The majority of reported cases are FIF anencephalic and/or acardic. The FIF is almost always single, but there are descriptions of cases with multiple fetuses, from 2 to 21 (16-27). In one case with three FIF, two of them were conjoined twins (28). It is possible that similar cases have been noted in clinical practice but not made known. At a time when a prenatal ultrasound diagnosis was not available, we, in fact, noticed in a 22-week-old stillborn a large head containing seven well identifiable embryonic structures, with numerous sketches of the lower limbs, all within an amorphous brain tissue.

Most FIF are present freely within the body of the host fetus without a defined sac like structure or umbilical cord. Their vessels are usually connected to the aorta or mesenteric circulation, the renal vessels, the middle sacral artery and the femoral artery of the host twin. In other cases a plexus where the FIF and the sac are both attached to the abdominal wall of the host twin has been observed (29). Moreover, the vascular supply may derive from several small vessels, the origin of which is rarely identifiable. According to some investigators, the vascular pedicle found in some cases of parasite fetus is not histologically an umbilical cord, but is a derivative of the right vitelline artery, that is the equivalent of the superior mesenteric artery and is constituted by an internal elastic lamina, vasa vasorum and nerves (15). Kang (30), however, described a case with an umbilical cord histologically normal and connected to the renal vein of the host with an amniotic-like sac, thus giving support to the theory of the included monozygotic twin. In addition, Chen (15) reported a case with a membranous capsule with nerves and with an umbilical cord containing a well-formed single umbilical artery and a vein. Heifetz (31) presented a case with nerve supply of the two vessels of the vascular pedicle and a membranous capsule, an internal elastic lamina and vasa vasorum in the artery of the pedicle.

Less frequently, one finds the FIF in a space containing a fluid or an amorphous material surrounded by a membranous capsule to which are connected by a vascular pedicle.

The membranous capsule consists of keratinized epithelium, or of endothelial cells, or of amnion and metaplastic squamous epithelium, or of cuboidal epithelium (22, 30, 32-34). Only occasionally has placental tissue been found at the origin of the vascular pedicle. Lamabadusuriya (35) described primitive chorionic villi with a central core containing blood vessels. And another case of “vestigial placenta” was reported by Farris (36).

**Intracranial FIF**

The intracranial location of the FIF is extremely rare. Only 17 cases, mainly with intraventricular location and hydrocephalus have been reported in the literature and these have been primarily in young patients (16, 19-21, 37-49). The prenatal diagnosis by ultrasound has been suspected in 8 cases (19, 20, 38-43). One case has been reported in two different papers by Miuta (19) and Saito (20). These FIF were suspected for the presence of one or more amorphous masses with calcifications associated with hydrocephalus, but without evidence of a vertebral structure or long bones. Only after birth, at autopsy or post-surgery was a diagnosis of FIF made, sometimes associated with a teratoma.

Only in one case (40), at 17 weeks of pregnancy, was the ultrasonographic prenatal diagnosis certain. It showed a fetus with multiple malformations (cystic hygroma of the neck and thanatophoric dysmorphia) with the presence in the posterior cranial fossa of a complex fetiform structure of about 40mm with a hyperecogenic skull. In this fetiform structure a weak rhythmic activity with a rate considerably lower than that of the host fetus could be detected by Doppler examination. This particular finding led to the diagnosis of FIF, confirmed after its delivery induced by administering prostaglandin. The autopsy examination of the parasite twin showed, in addition to a malformed univentricular heart, a gastrointestinal tract, liver, kidneys, upper and lower limbs with well developed digits and a vertebral column. A vascular pedicle containing a vessel, that starting from the anterior abdominal wall, was lost in a mass of amorphous and friable placental-like tissue which virtually replaced a large part of the brain. Interesting to note that the host twin with its multiple malformations differentiated from the other cases that very rarely presented any associated anomaly (Figure 2).

**Pathogenesis**

The pathogenesis of FIF continues to be debated and many theories have been proposed.

1. **Theory of germ cells**
   
   Under normal conditions, the primordial germ cells are detectable at the end of the third and at the beginning of the fourth week of pregnancy in the endoderm
of the wall of the yolk sac, near the origin of the allantois. Thereafter, they migrate in an amoeboid manner to the wall of the posterior intestine and then towards the gonadal ridge in the retroperitoneal area. If during this migration the germ cells are not topographically arranged in the normal way, they do not survive and are eliminated, probably with an immune mechanism (50). On the other hand, if they are isolated and survive, acquiring neoplastic property for oncogenic factors or mutant genes (51), they can become neoplastic totipotent germ cells. At this point they do not undergo involution and are not incorporated into the gonadal ridge, but they continue to have mitosis giving rise to teratoma or FIF. One objection to the theory of germ cells is the lack of explanation of the mechanism by which germ cells are responsible for the formation of FIF in the cranial cavity or in other sites far away from their normal migration to the retroperitoneum in the gonadal ridge.

2. Theory of unequal division of the blastocyst

It is hypothesized that the FIF is the result of an unequal division of the totipotent inner cells of the developing blastocyst. This results with the host embryo including the smaller cell mass and the initiation of a malformed monocorionic diamniotic twin or multiple FIF (52). This theory finds support in the fact that there has been an increased incidence of twinning in families of children with FIF. Also, the host twin and the fetiform mass are genetically identical with the same blood
group and the same set of chromosomes and the postnatal growth of the FIF in the host (17, 53).

3. Theory of monozygotic monocorionic diamniotic pregnancy

According to this theory, there is an adhesion of the two amniotic sacs and a subsequent adhesion with anastomosis of the vessels of the yolk sacs during the third week of pregnancy. There is successive twin to twin transfusion and progressive restriction and stunting of the smaller twin which is incorporated in the larger twin, becoming an included fetus (2, 10, 25, 32, 54, 55). This theory does not explain the association of a FIF with a teratoma or with multiple FIF.

4. Theory of the dicorionic diamniotic pregnancy

The anomaly could be related to a defective implantation of two blastocysts rather than to an abnormal twinning process (19, 30, 56). During the second week of pregnancy, one of the two blastocysts, instead of implanting in the endometrium of the uterine wall, may invade the extraembryonic mesenchyme of the other normally implanted blastocyst. Usually then the primary gastrulation develops in both embryos with the formation of two separate primitive streaks. But one embryo develops normally, while the other twin is reintegrated within the mesenchyme of the host, becoming a parasitic twin. This mechanism could explain the different sites of implantation of the FIF in the fetal mesenchymal components of the host twin. In addition, in the parasitic twin the differentiation of extraembryonic mesenchyme in the cardiogenic area does not happen with subsequent acardia. Furthermore, in the context of this abnormal process, some parasitic cells can initiate to form teratomas or fetiform multiple structures. It is important to remember that the primary extraembryonic mesoderm is a tissue that separates the primary yolk sac from the inner side of the trophoblast and, increasing in quantity, forms the extraembryonic coelom.

5. Parthenogenetic origin

The germ cells of the retroperitoneal region, where they are normally located, are parthenogenetically stimulated and develop a rudimentary fetus. Histocompatibility studies and genetic markers are not compatible with this etiology (57).

6. Theory of the acardic fetus

Studying the pathological aspects in about 1260 cases of conjoined twins, Spencer (12) noted their frequent association with FIF, acardic fetuses and teratoma. Being variations of an abnormal twinning of conjoined twins, these anomalous fetuses form a continuum resulting in: 1) a conjoined symmetric twin, 2) an externally attached parasitic twin, 3) an enclosed FIF, 4) an internal teratoma, or 5) an acardic fetus. It is important to note that rarely in these abnormal fetuses there is a normal brain or a functioning heart. The possible etiology, therefore, is a primary cardiac malformation with no possibility of growth and of independent living. However, the theory of the primary acardia is incompatible with reports in the current literature. At least 6 cases have been reported in which the presence of rudimentary cardiac structures were noted. Aslanabadi (58) noted a malformed heart in an oral FIF. Brand (14) described the case of a newborn with a FIF in the retroperitoneal cavity and a rudimentary heart. Kazez (59) reported the case of a two-month-old child with a sacrococcygeal mass containing a similcardiac form with a heart rate different from the rhythmic activity of the patient. De Lagausie (60) described the case of a baby delivered at 37 weeks by cesarean section who had a sacrococcygeal mass with the characteristics of a FIF containing a rudimentary heart, with contractile activity of a different frequency than that of the heart of the newborn. Mills (54) described an abdominal mass with the characteristics of a FIF detected at the 38th week of pregnancy. After delivery by cesarean section the prenatal diagnosis was confirmed. A color Doppler investigation showed a rudimentary heart in the FIF with contractile activity. Finally Ianriuberuto (40) described a 17-week-old fetus with multiple malformations and with an intracranial FIF containing a rudimentary heart with heartbeat of a different rate of that of its host.

7. Theory of secondary focus of development

This theory may explain the rare cases of intracranial FIF. The formation of a secondary focus of differentiation in the bilaminar embryo is assumed. Under normal conditions, at about 2 weeks of pregnancy the primitive line develops at the level of the bilaminar disk. At the cephalic pole of the line a thickening is formed which is the primitive node (Hensen’s node) that extends cranially. An invagination of the superficial cells in the node forms the blastopore, which in turn extends and becomes the notochord. If in proximity a second differentiation of a growing focus occurs in the same way as the primary focus, what results is a conjoined twin craniopagus. If the secondary focus is smaller and grows more slowly than the primary focus, it will be absorbed in the invagination of the cells of the host focus giving origin to a parasitic intracranial fetus (49). The intracranial FIF does not have a gestational
sac and in none of the reported cases has an amnion or chori-}

8. Theory of teratoma

The embryogenesis of the FIF continues to be debated because many authors believe that the anomaly is a very differentiated teratoma. Therefore, the two entities should not be separated, but considered two aspects of the same disease in different stages of maturation. Spencer (12) proposed that parasitic twins, FIF, teratomas and acardiacs all result from the deterioration or death of one embryo, the location of which often indicates the original site of attachment. The teratoma is a disorganized structure formed by pluripotent cells represented by all three germ layers that, unlike the FIF, do not develop after the primordial stage of germination stria. The result is the absence of formation of the notochord and of the spine. This difference is clinically important because the teratoma has considerable potential for malignancy, while rarely has there been reported a malignancy complication in the FIF (61). A case of a well-formed FIF associated with a malignant teratoma was presented by Du Plessis (62). There are but a few accounts of a teratoma associated with a FIF (29). In conclusion, whether the FIF is a highly differentiated teratoma or a parasitic twin remains controversial. Currently, according to the World Health Organization, the FIF is classified as a mature teratoma.

Conclusion

In this review published cases of FIF are examined, in particular the intracranial discovered in the prenatal period. Since the first prenatal ultrasonographic description of an abdominal FIF by Nicolin in 1983 (63), very few cases of this extremely rare congenital entity have been reported. At this time the prenatal diagnosis is still difficult because of the impossibility of differentiating a FIF from a more commonly occurring teratoma. Only occasionally, when a vertebral-like structure, or bones, or a heartbeat of a different rate than that of its host are found in the fetiform mass, is a diagnosis possible. The current information of the pathogenesis of this anomaly is still controversial. Further investigations, the rapid progress in the study of embryogenesis, pathogenesis and molecular data and the increase of observed cases with more sophisticated prenatal diagnostic techniques will allow for more comprehensive family counseling and for better management by obstetricians, neonatologists and pediatric surgeons.

References

5. Young GW. Case of fetus found in the abdomen of a boy. Med Chir Trans. 1809;1:234.