End-of-Life Issues at the Beginning of Life

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Ethical Aspects of Prenatal Diagnosis of Fetal Malformations

Article DOI: http://dx.doi.org/10.5915/43-9560
Video DOI: http://dx.doi.org/10.5915/43-9560V

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Abstract:

Fetal malformations complicate approximately 3% of all pregnancies. Many of these are minor or can be corrected after birth, but there are certain malformations that are lethal and others that are severe and others, that, even if corrected lead to permanent disability. Advances in prenatal diagnosis made possible the diagnosis of many fetal malformations. This led to the concept of the fetus a patient, independent of the pregnant woman, even though the moral status of the fetus is in dispute. Many of the lethal malformations are untreatable. However, for some, innovative in utero treatments, both medical and surgical, became possible. These interventions should be evaluated for the relative benefit and risk for both the fetus and the mother, because any such treatment has to involve the integrity of her body. This raises the ethical question of beneficence (to the fetus) versus the autonomy of the pregnant woman. The process of resolving this issue will be discussed, especially how to obtain a truly informed consent.

For the lethal malformations or for those severe or multiple malformations whose treatment is theoretically possible but the results of such treatment are unpredictable or may lead to life long disabilities and serious burdens for the infant or child and the family, prenatal counseling should include "prenatal advance directive" and a plan for palliative care, the components of which will be described.

Key words: Fetal malformations, prenatal diagnosis, prenatal counseling, fetal therapy, fetal surgery, medical ethics, palliative care.

Congenital malformations occur in 3% of pregnancies but are responsible for 20% of infant mortality. Many of the lethal or potentially lethal malformations can be prenatally diagnosed. However, despite the availability of elective abortions of fetuses diagnosed with these malformations, infants continue to be born with anomalies, either because they were missed, i.e. not prenatally diagnosed or they were diagnosed but therapeutic termination of preg-

nancy was not offered to the couple or if offered the couple did not choose it.

In this presentation I will start with a brief outline of the obstetric aspects of fetal malformations, namely their types, prenatal diagnosis, prognosis, and potential treatment. Then I will discuss the ethical aspects of dealing with these prenatally diagnosed malformations.

Obstetrical Aspects of Fetal Malformations

Types and Prenatal Diagnosis of Fetal Malformation

1. Chromosomal anomalies. Two methods are used for the diagnosis of chromosomal anomalies. The first is chorionic villus sampling (CVS), which entails sampling the villi that anchor the gestational sac to the inner lining of the uterus. The villus cells are embryonic cells, and their karyotype is that of the embryo. The procedure can be done early in the pregnancy, between 9 and 11 weeks. The second method for diagnosis is amniocentesis, a procedure whereby a needle is inserted in the pregnant uterus into the amniotic sac surrounding the fetus. A sample of amniotic fluid containing amniocytes is withdrawn. These are fetal cells, and their karyotype is the same as that of the fetus. This procedure is usually done between 14 and 20 weeks.

2. Genetic diseases. Some genetic diseases are caused by a single gene defect, for example, cystic fibrosis, sickle cell disease, inborn errors of metabolism, etc. These diseases are amenable to genetic testing. The tests could be of the gene itself if it has been identified or of the enzymes or hormones implicated in the disease. Diagnostic studies are indicated if we know that the mother had a previous child with the disease, if there is a family history of the disease, or if other tests showed that there is a high risk of the disease in the current pregnancy, for example if blood tests showed that both parents are carriers of an abnormal gene such as sickle cell trait. The studies can be accomplished by doing CVS as early as 9-11 weeks or, if CVS was not done, by an amniocentesis between 14 and 20 weeks. The studies can be done on the villus cells, amniocytes, or the amniotic fluid.

Other genetic diseases are not caused by a single gene but probably by interaction of multiple genes. These cannot be diagnosed by the above-mentioned genetic tests. An example of these are neural tube defects. Amniocentesis can diagnose these particular malformations by showing increased levels of alpha fetoprotein in the amniotic fluid.

3. Structural abnormalities that might not necessarily be associated with either chromosomal or known genetic defects can be diagnosed by imaging methods. The primary method during pregnancy is ultrasonography. During the first trimester, we can perform a vaginal ultrasound, which gives us a lot of information, but later on transabdominal sonography is the standard method. With the advent of three-dimensional ultrasound, we can see much more of the fetus' structures. Using the rendering technique, the external features of the fetus can be visualized, allowing the diagnosis of external malformations that hitherto could not be diagnosed. Magnetic resonance imaging (MRI) initially was not found to be useful because of fetal movements. Now, with the development of ultrafast MRI, it is a useful adjunct technique. It is used mostly to confirm a diagnosis or to add more specificity and details to the diagnosis made by ultrasonography.

Even with all these advances, there are still many malformations that cannot be diagnosed prenatally. More detailed discussions of these topics have been published.[1-6]

Lethal and Potentially Lethal Malformations

Ultrasound can diagnose lethal malformations such as anencephaly or acrania as early as the first trimester. In these conditions, there is a failure of development of the brain and the overlying skull. These fetuses will not survive. Also, by using CVS at 9-11 weeks, we can diagnose many of the lethal malformations. The primary examples are trisomy 13, trisomy 18, and triploidy, although the latter is very rare. Also, we can diagnose early on some genetic diseases such as Tay Sachs disease and spinal muscular atrophy type 1, in which the babies can survive for a few months to a couple of years.

Unfortunately, these chromosomal malformations and genetic diseases cannot be treated or corrected. If they are not diagnosed in the first trimester, they can be diagnosed in the second trimester by amniocentesis and performing the studies on the amniocytes.

Yet there are different lethal malformations that cannot be diagnosed except in the second trimester using the imaging techniques provided by ultrasound, three-dimensional ultrasound, or rapid

acquisition MRI described above. Examples of these lethal malformations include bilateral renal agenesis, where the kidneys are not developed at all, and bilateral multicystic or dysplastic kidneys, where the kidneys are there but functionless. There is no treatment for these conditions, and we know these fetuses or babies cannot survive. There are many other examples of these lethal malformations that can only be diagnosed in the second trimester.

On the other hand, there are some other potentially lethal disorders and structural malformations that are amenable to treatment, and that is what we need to discuss. For example, *hydrops fetalis* is a disorder characterized by generalized edema of the subcutaneous tissues and accumulation of fluid in the serous cavities, that is the pleural, the pericardial, and the peritoneal cavities. The most common cause of this condition used to be Rh blood group incompatibility (isoimmunization). Now, other blood group incompatibility conditions, for example anti-Kell isoimmunisation, are becoming more frequent. These are all called immunologic hydrops, to be distinguished from nonimmunologic hydrops, which, for example, occurs secondary to fetal complete congenital heart block or to cardiac structural anomalies, either left or right hypoplastic heart. Other causes of nonimmune *hydrops fetalis* include sacrococcygeal teratoma and severe fetal anemia caused by massive fetomaternal bleeding or parvovirus infection, conditions that in effect cause high output cardiac failure.

Fetal Therapy

The fact that at least some of the potentially lethal malformations can be treated prenatally led to the development of the new field of medicine, fetal therapy. This can be divided into medical therapy, surgical intervention, and fetal surgery.

Medical Therapy

Medical therapy, examples of which are the treatment of congenital adrenal hyperplasia by dexamethasone, the treatment of suprarventricular tachycardia by digoxin and the use of dexamethasone for the treatment of fetal complete heart block in women with collagen vascular disease, i.e. lupus erythematosus or Sjorgen syndrome, who have Ro antibodies.

Surgical Intervention

An example of surgical intervention is the intrauterine, intraperitoneal, or intravenous red blood cell transfusion. These transfusions are used for the treatment of blood group isoimmunization (Rh, Kell, etc.) that results in severe hemolytic anemia. Minor fetomaternal bleeding occurs in most pregnancies, but occasionally the fetus significantly bleeds in its mother, resulting in severe anemia that leads to *hydrops fetalis* or even to fetal death. If this condition is diagnosed, then one can transfuse the fetus *in utero*. A fetus acquiring parvovirus infection can sometimes develop severe anemia secondary to bone marrow depression that may lead to heart failure and, if untreated, death. Intrauterine transfusion is life-saving in these conditions.

Other examples of surgical intervention include intrauterine stem cell transplants that have been used in the treatment of severe combined immune deficiency and placement of a pacemaker for cases of congenital heart block that do not respond to medical treatment. Another example of surgical intervention is thoracocentesis for the treatment of pleural effusion, whereby a needle is inserted through the uterus into the fetal thorax to aspirate the fluid. Alternatively, a thoraco-amniotic shunt is placed for continuous drainage of the pleural fluid into the amniotic fluid. Another example is laser coagulation of communicating placental vessels in the treatment of twin-twin transfusion syndrome (TTTS).[7]

Fetal Surgery

Fetal surgery involves making an incision in the maternal abdomen and then a uterine incision as for a cesarean section. Then, instead of delivering the whole fetus, the surgeon delivers only the part of the fetus that needs the operation. For example, if the indication is a sacrococcygeal teratoma, the surgeon delivers only the lower back of the fetus and tries to excise the tumor. On the other hand, if the indication is a diaphragmatic hernia, the surgeon exposes the thorax. After the operation is completed, the fetus is returned entirely into the uterus, the fluid is replaced, and the uterus and maternal abdomen are sutured.

Fetal surgery has been possible due to advances in fetal imaging, as one can know the exact diagnosis, the exact location of the tumor or the diseased organ, and the exact location for the incision, etc.

Obviously, advances in maternal anesthesia are very important for the success of the surgery. As are advances in the technical aspects of surgery, such as the availability of special instruments and special staples, which make such surgery possible. Another significant factor that enables the performance of fetal surgery is the advance in tocolysis, the suppression of uterine activity. The most serious complication of fetal surgery is that the patient may go into preterm labor postoperatively. Therefore, if we are going to operate on a 22-week or 23-week fetus, and the patient goes in labor and delivers, then the fetus will die from prematurity rather than from the primary disease. Because we now have good tocolytic agents that can stop uterine contractions after the surgery, it has become less risky.

However, fetal surgery is still a very serious procedure that requires great expertise and a well-coordinated team. Fetal surgery is indicated only for the treatment of serious or potentially lethal anomalies when *in utero* correction allows more normal fetal development and a better chance of survival than neonatal surgery. These surgical procedures can be done after the baby is born, but if they are done in utero, there will be much better chance for the fetus or neonate to survive. Examples of when fetal surgery is indicated include bladder outlet obstruction, sacrococcygeal teratomas, and congenital diaphragmatic hernia. Further details have been published.[4-9]

Ethical Issues when Dealing with Fetal Malformations

Moral Status of the Fetus

The first question we need to address is whether the fetus has a moral status. If we assign an independent moral status to the fetus, this generates obligations to the fetus on the part of both the pregnant woman and the physician. There is no agreement about when the fetus acquires independent moral status. Some believe it to be at the time of conception at which time the fetus is a "full human being." Another school of thought gives the fetus a graded moral status. In that view the fetus has some sanctity, but in the beginning it is not that much. As the fetus develops, it gradually becomes more morally independent. Other ethicists believe that the fetus becomes a moral person only at the time of birth.

In Islam we generally equate the moral status with ensoulment, i.e. the breathing of the soul into the fetus. The majority of scholars believe that this happens at 120 days after conception.[10,11]

With advances in prenatal diagnosis of fetal malformations, and the availability of treatment, whether medical or surgical as discussed, a new discipline of medicine has developed, fetal medicine, and the fetus by that definition is considered a patient. That raises a question. If one does not consider the fetus a moral person, how come he or she can be a patient? There is general agreement that regardless of the moral status of the fetus, a patient is defined as an individual towards whom a physician has beneficence-based ethical obligation. By that definition we can call the fetus a patient.[12,13] Considering that the fetus is a patient does have some ethical implications. What are these?[12-14]

Ethical Principles as Applied to Fetal Therapy

In the fetus, beneficence-based obligations exist as diagnostic or therapeutic interventions performed are reasonably expected to result in a greater balance of good over harm at the time of the intervention or later after birth. Ethicists argue that as long as there is no agreement on the independent moral status of the fetus, there is no autonomy-based obligation to the fetus. It is important to understand that prenatal care is unique in that it has dual goals of a good outcome for two individual patients and particularly because access to one, that is the fetus, has to be through the other, that is the pregnant woman. So we have a dual obligation, and in all ethical deliberations, both the interests of the mother and the fetus should be considered. The beneficence-based obligation to the fetus must be balanced with the beneficence-based and autonomy-based obligations to the mother. The fetus does not have an autonomy-based obligation, but the mother does; therefore, we have to balance all these factors.

What are the ethical criteria we use for fetal therapy, especially for fetal surgery, which is much more serious? First of all, there should be a very high probability of being life-saving or preventing serious or irreversible disease, injury, or handicap to the fetus or the child to be. Also, there should be low mortality risk for the fetus and low or manageable risk of serious disease, injury, or handicap to the fetus or born child. More importantly, the mortality risk to the mother should be negligible or very low, and the risk of disease or injury or handicap to the

mother should also be low and definitely has to be manageable. We do not risk the life of the mother for that of the fetus.

The importance of getting a truly informed consent before contemplating fetal therapy and especially fetal surgery follows from this discussion. The natural instinct of the mother is usually to sacrifice for the well-being of her baby. This should not be used as an excuse to avoid having a real, detailed informed consent. The pregnant woman should be given all the facts: the benefit and risk to the fetus including long-term prognosis for the fetus and newborn. She also should be apprised of factors affecting her own fertility and subsequent pregnancies, especially after fetal surgery, which in effect is a miniature cesarean section. All subsequent deliveries have to be by repeat C-section with additional risks. The mother should exercise her autonomy to accept or refuse, taking into consideration her beneficence-based fiduciary and ethical obligation to her fetus. As long as she decided not to abort, she does have certain obligations to the fetus that she is bearing. To safeguard the mother while obtaining consent, the physician obtaining the consent should be impartial, preferably not a member of the fetal medicine team. The mother's own physician, the primary physician, has to help her to reflect on her risks, and other family members, particularly the father of the baby, should be involved. There should be an independent review by the institution review board (IRB). Ethics consultation is a good idea, even if the contemplated procedure is not "investigational." Occasionally, psychiatric consultation is needed if there is any doubt about the emotional status of the mother.

Prenatal Counseling

Prenatal counseling of the woman bearing a malformed fetus should include the nature of the defect, the prognosis for fetal survival, any potential long-term disability and possible treatments, whether medical or surgical, and their risks along with a discussion of the consequences of no treatment. These points should be discussed in as much detail as possible with as much information as available. Consultation with the neonatologist who is going to take care of the newborn is essential. In addition to that, consultation with other pediatric specialists, for example pediatric surgeon, neurologist, and urologist, depending on the particular malformation, should be offered. The counseling team, in addition to these physicians, should include neonatal nurses, social workers, and clergy. The counseling should be sensitive to the mother's religious and cultural beliefs, especially those related to dying and death. If surgery is an option, the patient should be referred or at least offered referral to a tertiary care center with expertise in the specific anomaly. Not all centers in the country are expert in the different anomalies.

Palliative Care

If the decision against active fetal or neonatal therapy is made, then offering palliative care is the ethical thing to do. The counseling needs to move beyond simply giving facts or just doing what the patient wants. The best interest of the not-yet-to-be-born-child should be considered. We have to remember that sometimes outcomes may be worse than death for the baby.[15] Also, the burdens of therapy can be greater than the potential benefits, such as cases with left hypoplastic heart or large meningomyelocele associated with hydrocephalus. Counseling, therefore, should include the option of palliative care, which should be offered if a definite lethal anomaly is diagnosed or a named diagnostic anomaly is uncertain although its association with poor prognosis is definite. For example, we know that significant pulmonary hypoplasia, i.e. underdeveloped lungs, occurs in certain types of skeletal dysplasia. We do not have to know the exact type of skeletal dysplasia, but, if the thorax is so small, we know the lungs will not develop.

Palliative care should also be offered even in cases where the fetus is not malformed, but a lethal prognosis is definite, for example, pulmonary hypoplasia associated with prolonged premature rupture of membranes where all the amniotic fluid is lost and there is no fluid around the fetus (anhydramnios) beginning at 16 weeks or 18 weeks. In these situations, we know with almost 100% certainty that this fetus will have severe pulmonary hypoplasia and will not be able to breathe or survive. Palliative care in such circumstances is a "prenatal advance directive" akin to the one we advocate for adults.

Specific issues need to be discussed in these cases. We have to decide on the place of delivery. Will it be a community hospital or a tertiary care

hospital? Who will be the delivering physician? Will the delivering physician be her own obstetrician or a maternal fetal medicine specialist?

The mode of delivery is important to decide. Will it be a vaginal delivery? This may be the best option, but sometimes a planned Cesarean section is better because of the possibility of obstructed labor if we are dealing with a big tumor or hydrocephalus or when it is important for the mother to be able to hold the live baby even for a few minutes. We know that many of these babies who have severe pulmonary hypoplasia or severe malformations will breathe for a couple of minutes and then die. We also know that many of these babies will die in the process of natural labor. Some mothers may opt for Cesarean section just to be able to hold their living baby, even for few minutes.

The timing of delivery is also important. Scheduled delivery offers a lot of advantages. Earlier delivery may decrease the risk of maternal complications. For example, hydrops fetalis can be associated with preeclampsia, so it is better to deliver early to avoid this complication. Premature rupture of membranes is associated with a risk of maternal infection. Earlier delivery will decrease this risk. Also, timing the delivery enables all the family members the mother wants to be present at this stressful time, as well as the clergy of her choice, and ensures the availability of appropriate resources.

Timing of the delivery is also important because many of these fetuses can die *in utero*. Therefore, it is a good idea to plan the delivery before the fetus dies. From the psychiatric point of view, it is also important because, while some women may enjoy the extra time with a baby still living in their wombs, others will feel bad about it. They would be distraught with the fact that their baby will die at any time. They are afraid of facing comments by bystanders, people in the grocery store, who may ask "How is your pregnancy?" or "How is motherhood?" or "When is the baby due?" So some women want to be delivered sooner, while others may want to be delivered later. We have to take all these factors into consideration for the timing of delivery.[16-19]

There are other issues to be considered postpartum. The mother should be in a separate room away from the postpartum floor. The room should provide easy access to the medical team. Additional diagnostic studies may be necessary, for example, testing the cord blood, skin biopsy, or autopsy. It is important to remind the mother and the family that although the newborn is going to die, it is not possible to predict if that will happen after hours, days, or occasionally a few weeks. They should be aware that this is possible. It will alleviate some of their anxiety and anticipation. Further, plans for discharge and hospice care should be made as conditions become clearer.

Autopsy is very important because in 10-14% of these cases a new diagnosis that was missed prenatally will be discovered. Often, secondary diagnoses will be added. This will give feedback to the maternal fetal medicine doctor on the accuracy of prenatal diagnosis and improve the accuracy of the epidemiologic studies. It will also improve the estimation of the risk of recurrence. Autopsy will establish the precise cause of death and thus will alleviate any guilt feelings by reassuring the parents of the inevitability of the death.

After discharge, follow up visits should be scheduled. Ideally these include a nurse going to the family's home. If this is not possible, follow up by phone is essential. A postpartum visit with the physician should include, in addition to the regular physical examination, a discussion of the recurrence risk based on all available information, whether known prenatally or gathered postpartum from the additional tests and autopsy results. Plans for future pregnancy and any preventive measures should be discussed. For example, if the baby had a neural tube defect, supplemental folic acid before a next planned pregnancy significantly reduces the risk of recurrence.[20]

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