Ethical and Medical Considerations in the Treatment of Ectopic Pregnancy

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The incidence of ectopic pregnancy is on the rise and accounts for approximately 2% of all pregnancies in the United States. Incidence has increased six-fold over the last two decades. Ectopic pregnancy is the leading cause of maternal mortality in the United States in the first trimester, and accounted for thirty-five deaths in 1997. But beyond the medical implications of ectopic pregnancy, it also has ethical considerations that need to be taken into account. The Ethical and Religious Directives for Catholic Health Care Services states that: "Catholic health care ministry witnesses to the sanctity of human life ‘from the moment of conception until death.’" Yet in contrast to this, current medical practice for the treatment of ectopic pregnancy consists of modalities that could constitute a direct abortion. What is a Catholic physician or hospital to do in treating a woman with an ectopic pregnancy? How are we to be witnesses to the sanctity of life in this tragic problem? This presentation is intended to address the medical and ethical concerns in the treatment of ectopic pregnancy.

Ectopic Pregnancy Defined

An ectopic pregnancy is the implantation of the embryo outside of its normal intrauterine site. Subsequent growth of the embryo occurs for a variable length of time before the clinical signs and symptoms of an ectopic pregnancy become manifest, depending on the site of implantation. Sites of ectopic implantation are the fallopian tube (95-97%), interstitial/
cornual angle (2-4%), ovary (0.5%), abdominal cavity (0.3%), or cervix (0.1%). Clinical signs and symptoms occur at about six to eight weeks after the last menstrual period in a tubal pregnancy and at ten to twelve weeks in an interstitial/cornual angle pregnancy. In the majority of cases of ectopic pregnancy, presenting symptoms are secondary to tubal rupture or tubal leaking. Abdominal ectopics can proceed to viability in 11 – 45% of cases, but maternal mortality from massive hemorrhage is not uncommon. Etiology of ectopic pregnancy includes tubal damage secondary to pelvic inflammatory disease, intrauterine devices, progesterone-only pills, two or more elective abortions, ART, previous ectopic pregnancy, tubal scarring from any cause, and hormonal abnormalities. Evidence of pelvic inflammatory disease is present in up to 77% of fallopian tubes with an ectopic pregnancy.

Due to the advancement of the diagnostic studies available, the diagnosis of an ectopic pregnancy is made much earlier in its course than in years past, and has lead to a decline in maternal mortality. These diagnostic studies include sensitive β-HCG assays, trans-vaginal ultrasound, progesterone assays, and laparoscopy. These diagnostic advancements have largely replaced the classic triad of pain, bleeding, and adnexal mass in the definitive diagnosis of ectopic gestation.

The diagnosis of ectopic pregnancy is based upon the accurate detection of β-HCG, a hormone produced by the syncytiotrophoblasts of the embryo. β-HCG levels are detectable in the blood as early as six days after conception and are always present by twelve days after conception. β-HCG levels approximately double every forty-eight hours in early pregnancy; an abnormal rise of β-HCG is suggestive of miscarriage and ectopic pregnancy.

At levels over 2000 mIU/ml, a gestational sac should be seen in the uterus by trans-vaginal ultrasound, although in cases of multiple gestation there can be a delay of visualization of the gestational sac. Progesterone levels are also useful predictors of normal intrauterine gestations, ectopic pregnancy, and spontaneous abortion, especially when used in conjunction with β-HCG levels and trans-vaginal ultrasound. Progesterone levels <5 ng/ml are highly suggestive of a miscarriage or ectopic pregnancy. Trans-vaginal ultrasound is a highly useful tool in the diagnosis of early intrauterine pregnancies, and when used in conjunction with β-HCG levels, gives physicians the ability to often make the diagnosis of ectopic pregnancies without the need for laparoscopy or laparotomy. Intrauterine gestational sacs can be seen by trans-vaginal ultrasound as early as sixteen days post conception, and embryonic cardiac activity can be seen shortly thereafter.

Unlike years past, most cases of ectopic pregnancy today are diagnosed before tubal rupture has occurred, without the need for surgical
exploration to stop life-threatening bleeding. The early diagnosis has also lead to the trend to treat ectopic pregnancy by way of laparoscopy or with medication. Current treatment modalities for ectopic pregnancy are: 1) expectant management; 2) surgical management (salpingostomy or salpingectomy); 3) medical management (methotrexate).

Expectant management is a sound option for early ectopic pregnancies that have relatively low β-HCG levels. The ectopic tissue gradually degenerates over time and is eventually reabsorbed. Criteria for expectant management are: stable vital signs; β-HCG levels less than 1,000-2,000 mIU/ml and falling; mass size less than 2-4 centimeters; and less than 50 ml of hemoperitoneum. Successful resolution rates range from 60-64% if the above criteria are met. If levels are above 2,000 mIU/ml, the failure rate is 93.3%. Benefits are that the patient avoids any surgical or medical treatment with the inherent risks. Risks include tubal rupture and failure for spontaneous resolution and the need for further intervention.

Three Types of Management

The first type of surgical management is laparoscopic salpingostomy, which is now deemed the surgery of choice for the treatment of an unruptured ectopic pregnancy. A linear incision is made in the anti-mesenteric portion of the fallopian tube, and the gestational tissue is removed. The tube is left open to heal by secondary intention, hopefully allowing tubal patency and function to be preserved. Future pregnancy rates are reported to be between 50 – 67% , but repeat ectopics occur about 7-16% of the time. Risks of linear salpingostomy are that trophoblastic tissue may be left behind leading to a condition of a “chronic ectopic”, where trophoblastic tissue continues to remain viable. A chronic ectopic occurs about 5-20% of the time following linear salpingostomy.

The second type of surgical management is salpingectomy. Partial or total salpingectomy is still the procedure of choice in ruptured ectopic pregnancy. Part or all of the tube is removed via the laparoscope or laparotomy. Future pregnancy rates for patients undergoing salpingectomy depend on the condition of the remaining tube, and range between 30-80%. There is no chance of persistent ectopic. Re-anastamosis of the tube may also be offered in patients who undergo a partial salpingectomy, either at the initial surgery or at a later time.

The third type of management for ectopic is medical management, which involves the systemic injection of methotrexate. Methotrexate is an anti-metabolite, and its site of action is the rapidly dividing outer trophoblastic tissue of the embryo. After the trophoblastic tissue is eliminated, reabsorption of the tissue occurs and hopefully tubal patency and function are preserved. Toxicity of methotrexate can occur in 20-30%
of patients, depending on whether single or multiple dose regimens are used. Methotrexate fails to eliminate the ectopic pregnancy in 5-29% of cases. Failure is more likely to occur if cardiac activity is present, β-HCG levels are >3,000-5,000 mIU/ml, and progesterone levels are >10 ng/ml. Patients who received systemic methotrexate therapy had a more negative impact on their quality of life (secondary to the side-effects of the medication) than did patients undergoing surgical management. Methotrexate therapy would be preferred by most patients, even with the negative side-effects, but only as part of a completely non-surgical management strategy. Future pregnancy rates following methotrexate are comparable to salpingostomy (50-67%).

In the current management strategies for ectopic pregnancy, controversy still exists over the best treatment modality. Despite the push by many gynecologists for tube-sparing surgery (salpingostomy) or medical management (methotrexate) of ectopic pregnancy, these methods have not been shown to be superior to salpingectomy in terms of future pregnancy rates.

The condition of the contra-lateral tube and a history of previous tubal surgery are the most important factors in determining subsequent pregnancy rates, not the treatment modality chosen. If the contra-lateral fallopian tube was normal and there is no past history of tubal surgery, pregnancy rates are about 70%. If the contra-lateral fallopian tube is abnormal, the pregnancy rates are only 30-40%. One advantage of salpingectomy is that it avoids any potential of a chronic ectopic. In a patient with an ectopic pregnancy in her only remaining tube, however, tube-sparing surgery, methotrexate, or partial salpingectomy with reanastamosis (by surgeons with proper training) are the only options that allow for preservation of future fertility. An advantage of methotrexate is that it offers the patient a completely non-surgical intervention for ectopic pregnancy, which is an attractive option for some patients.

The Catholic teaching with regard to ectopic pregnancy places the life of the mother and the life of the unborn child on an equal plane from the moment of conception. "No physician or moralist would admit that it is lawful to kill the mother in order to save the life of the child; so also it is unlawful to kill the child in order to save the life of the mother." Three directives are stated in the Ethical and Religious Directives for Catholic Health Care Services that apply to ectopic pregnancy. Directive 47 states: "Operations, treatments, and medications that have as their direct purpose the cure of a proportionately serious pathological condition of a pregnant woman are permitted when they cannot be safely postponed until the unborn child is viable, even if they result in the death of the unborn child." Directive 48 states: "In case of extra-uterine pregnancy, no intervention is morally licit which constitutes a direct abortion." What
constitutes a direct abortion is stated in Directive 45. “Abortion (that is, the directly intended termination of pregnancy before viability or the directly intended destruction of a viable fetus) is never permitted. Every procedure whose sole immediate effect is the termination of pregnancy before viability is an abortion, which, in its moral context, includes the interval between conception and implantation of the embryo.” Essentially, the directives state that any treatment of an ectopic pregnancy is morally permissible as long as it does not cause a direct abortion, even though it may result in an indirect abortion.

How then do we treat the maternal life-threatening condition of an ectopic pregnancy while not causing a direct abortion? Catholic ethicists have used the principle of double effect to explain the licitness of salpingectomy in the treatment of ectopic pregnancy. The principle of double effect states: 1) The action, considered by itself and independently of its effects, must not be evil; 2) The evil effect must not be the means of producing the good effect; 3) The evil effect is sincerely not intended, but merely tolerated; 4) There must be a proportionate reason for performing the action, in spite of its evil consequences. The principle applies to ectopic pregnancy in the following way. The removal by salpingectomy of a pathologically diseased tube is not an evil action of itself. The death of the embryo (the evil effect) does not produce the saving of the mother’s life (the good effect). The evil effect of the death of the embryo is not intended. The life-saving procedure for the mother is proportionate to the loss of the embryo. On the other hand, salpingostomy and methotrexate have been seen as direct attacks on the embryo, and thus have not been viewed as licit treatments.

**Recent Debate on Salpingostomy and Methotrexate**

Recently, a debate has surfaced in the Catholic ethical literature over whether salpingostomy and methotrexate can be legitimately used in the treatment of ectopic pregnancy. Rev. Albert Moraczewski in the June and August 1996 issues of *Ethics and Medics* gave arguments in favor of the legitimacy of salpingostomy and methotrexate in the treatment of ectopic pregnancy. His arguments state that both procedures essentially act by causing an indirect abortion, which if true would be morally acceptable options. His argument in favor of salpingostomy states that “to remove the pathological tissue in such a manner that part of the tubal wall remains.” Rev. Moraczewski is essentially arguing that a salpingostomy is actually more of a “micro” partial salpingectomy. “This maneuver extracts a sizable amount of damaged tubal tissue... the embryo proper is also removed.” This argument does not apply for the following reasons. First, Stock in his study of 110 tubal gestations found that growth of the ectopic occurs in
mostly an intra-luminal location. In a salpingostomy, the incision is made into the tubal lumen, and the ectopic gestation is grasped and usually easily expressed out of the lumen, and “care should be taken to avoid trauma to the mucosa.” The maneuver is intended to remove only the ectopic gestation, not a “sizable” amount of the tube. Also, salpingostomy works because trophoblastic tissue has a loose “attachment” to maternal tissue during the first trimester. True “attachment” to maternal tissue actually occurs only in the second trimester. The salpingostomy procedure essentially only removes the ectopic pregnancy itself, not damaged tubal tissue.

Rev. Moraczewski’s argument in favor of the use of methotrexate basically states that the intention is to “stop the destructive action of the trophoblastic cells,” with the unintended effect being the death of the embryo. The trophoblastic layer (the future placenta) of the embryo is the largest functioning organ of the embryo, and remains so until delivery of the infant. The trophoblast is just as integral to the life of the embryo as the heart is at this time. A direct attack on the trophoblast with methotrexate would be equivalent to a direct attack on the heart with potassium chloride.

Dr. William May, in the March 1998 issue of *Ethics and Medics*, gave arguments against the use of salpingostomy and methotrexate, stating that they would constitute a direct abortion. Dr. Eugene Diamond, in the August, 1999 issue of the *Linacre Quarterly*, gives an excellent paper on the topic of ectopic pregnancy, and also sides against the use of salpingostomy and methotrexate.

Salpingostomy and methotrexate are interventions which constitute a direct abortion, *but only when* a living embryo is present inside the trophoblast. If an embryo never develops or has developed but is now “dead,” then salpingostomy and methotrexate would constitute licit means of treatment of ectopic pregnancy. In order to understand this concept better, a review of basic embryology is necessary, as well as a concept of what constitutes human death before heart activity is present in the embryo.

Fertilization of the ovum by the sperm usually occurs in the ampullary portion of the fallopian tube. The whole process of fertilization, with the combining of the chromosomal material, takes about twenty-four hours to complete.

This one cell human life is called the zygote. This zygote begins to divide into daughter cells called blastomeres, shortly after fertilization is completed. Over the next two to three days, while being propelled through the fallopian tube by ciliary action and peristalsis, the blastomeres continue to divide. Up to the eight to sixteen cell stages, all the blastomeres are totipotential, that is that each one is capable of forming an entire new human life, as in the case of monozygotic twins.
When the cells number twelve to fifteen, the name morula is used. The morula reaches the uterus on about day three or four after fertilization. A fluid-filled cavity begins to form in the morula, causing the blastomeres to form into an outer cell mass and an inner cell mass. The outer cell mass or trophoblast will form the chorion and future placenta. The blastomeres of the inner cell mass will give rise to the body structure, the amnion, and the yolk sac. This is a very important stage of differentiation, which will be expanded upon later. The blastocyst free-floats in the uterine cavity for the next three days, continuing to grow and divide, slowly shedding the acellular covering called the zona pellucida.

By the sixth day after fertilization, the outer layer of the trophoblast begins to implant into the uterine cavity. The total implantation process into the endometrial lining takes until the twelfth to thirteenth day after fertilization. By day fourteen, the primary chorionic villi start to develop and the entire blastocyst measures about 3-4 millimeters. Rapid growth of the trophoblast and the body of the embryo occurs now so that by post-conception day twenty-one, the embryonic body measures about 1.5-3.0 millimeters and the chorionic sac measures about 4-5 mm. By post-conception days twenty-one to twenty-two, embryonic cardiac activity is present, and can be detectable by trans-vaginal ultrasound almost as early as it appears. By the twenty-eighth day after conception (six weeks since the first day of the last menstrual period on a twenty-eight day cycle), the embryonic body measures 4-6 millimeters in size and the chorionic sac measures 1.5 centimeters. The embryonic body now has visible upper and lower limb buds, otic pits (future ears) and lens placodes (future lenses of the eye) are also visible. The embryonic body and trophoblast continue to grow rapidly, and by the end of the eighth week all major organ systems have formed. At the beginning of the ninth week, the fetal period starts.

**Human Life is Now Present**

Given this very brief overview of embryology, it is important to discuss what constitutes human life and human death before the initiation of embryonic cardiac activity. Human life is present at the moment of conception when the zygote is formed, and continues as long as the zygote is alive. Human life continues to be present in the morula and blastomere stage of development as long as any of the totipotential blastomeres are alive, since each can develop into a human being (as in twins). When the blastocyst forms, an important differentiation takes place, the creation of the inner and outer cell masses. Once this division takes place, an outwardly visible organizational structure is made (although it is inwardly present from the moment of conception). The inner cell mass contains the
cells that develop into the body structure. The outer cell mass or trophoblast are the cells which form the future placenta.

The terminology in this area is sometimes very confusing because the term “embryo” can refer to the entire entity (inner and outer cell masses) or it can refer to only the embryonic body structure. For purposes of this paper, after differentiation into the inner and outer cell masses, I will refer to the body structure as the embryonic body, or sometimes as just the embryo.

A hierarchy of the parts is now made, with the embryonic body of the inner cell mass being the central part, and all the other structures being “organs” of the embryonic body. After the point of division into the outer and inner cell masses, human life is present as long as the embryonic body develops and continues to grow. If the inner cell mass does not form, or forms but stops growing and degenerates, then human life is no longer present.

Failure of the development of the inner cell mass with continued growth of the outer cell mass (trophoblast) leads to the clinical entity of a “blighted ovum”, now called an anembryonic pregnancy. Essentially, it is an empty gestational sac, without embryonic body development. The inner cell mass for some reason does not develop, while the more resilient outer cell mass (trophoblast) does. Newer research in this area shows that total failure of any formation of the inner cell mass cells is probably not exactly the case. The cells of the inner cell mass do develop for a short time, but then stop and degenerate, while the trophoblastic tissue continues growth for a variable length of time. This is an important concept, because it has implications in ectopic pregnancy.

In a tubal pregnancy, implantation of the blastocyst occurs with the invasion of the inner tubal mucosa by the trophoblast. As the ectopic grows, there is distention of the fallopian tube, and eventual erosion into the arteries of the fallopian tube. The distention of the tube and/or the bleeding causes the symptoms of pain.

Yet unlike the normal embryological development present with an intrauterine pregnancy, an ectopic pregnancy very often lacks an embryo. In a review of the prospectively done pathological studies of ectopic pregnancy in the literature, an embryo detection rate of only 14-39% was reported. The majority of ectopics only contain an empty chorionic sac, disorganized trophoblastic tissue, or hemorrhage without identifiable tissue. In the largest of these studies, Poland et al. found only 58 cases which contained an embryo or fetus out of 411 ectopic specimens (14%). DiMarchi et al. found 20 out of 131 cases (15%) to have an embryo present. If the numbers from all the studies are combined, 117 out of 656 (17>8%) contained an embryo or fetus. Emmrich and Kopping, in a study of 329 tubal pregnancies, found changes in the trophoblastic villi
that were consistent with blighted ovum or transition to blighted ovum in 84.5% of cases. They suggest that the unfavorable conditions for nidation in the fallopian tube have a decisive role in the embryo failing to develop in ectopic pregnancies.

Based on these findings, most ectopic pregnancies have had embryonic death occur. If embryonic death is present, then any treatment modality can be used, including salpingostomy and methotrexate. The criteria for making the diagnosis of embryonic death in ectopic pregnancy have not been previously defined or well studied (other than lack of cardiac activity in an identifiable embryo). Can we reliably diagnose which ectopic pregnancies have a living embryo and which have had embryonic death?

**Current Diagnostic Capabilities**

The following is an assessment of the current diagnostic capabilities. Some physicians may disagree with this assessment. In utilizing the current diagnostic studies of sensitive β-HCG assays, trans-vaginal ultrasound, and progesterone assays, ectopic pregnancies can be divided into one of three categories: 1) embryonic life is present; 2) embryonic death has occurred; and 3) unable to determine if embryonic life or death is present.

First let us consider the case where embryonic life is present based upon current diagnostic studies. Cardiac activity visualized by ultrasound in an ectopic pregnancy is a definite sign of embryonic life, thus human life is present. Cardiac activity is reported to be visualized by trans-vaginal ultrasound in 15-28% of patients with an ectopic pregnancy.\(^{41,42}\) Brown and Doubilet\(^{43}\) in a meta-analysis showed that an adnexal embryo with a heartbeat can be seen in 99 of 492 patients (20.1\%) with a known ectopic pregnancy. These numbers closely correlate with the probability of finding an embryo in ectopic pregnancies based on the pathological studies. If a living embryo is present outside the uterus, it will be most likely found by trans-vaginal ultrasound.

Second, let us consider the case where embryonic death has occurred based on current diagnostic studies. When the diagnosis of ectopic pregnancy (the diagnosis of ectopic pregnancy is a topic in itself and will not be addressed in detail) is highly suspected based on the clinical information and embryonic cardiac activity is not seen on trans-vaginal ultrasound, the following criterion is evidence that embryonic death has occurred: a progesterone level <5 ng/ml and β-HCG levels that are not appropriately rising (<25% rise over two days).

McCord et al.\(^{10}\) retrospectively studied 3,674 pregnancies and divided the patients into three pregnancy outcomes: viable intrauterine pregnancy, spontaneous abortion, and ectopic pregnancy. They found that a viable intrauterine pregnancy occurred in only 2 of 1,279 patients (0.16\%) with
serum progesterone level <5 ng/ml, but both of these patients had normally rising \( \beta \)-HCG levels. Hahlin\(^{44} \) found that no normal intrauterine pregnancy had both a progesterone level of <30 nmol/l (9.4 ng/ml) and an abnormal increase in \( \beta \)-HCG, whereas 72% of ectopic pregnancies and 81% of spontaneous abortions had both of these laboratory results. The other 28% of ectopic pregnancies are those with a higher progesterone level and/or normally increasing \( \beta \)-HCG levels. These are the pregnancies that are most likely to contain a living and growing embryo. Ectopic pregnancies with a living embryo have a higher mean \( \beta \)-HCG level\(^ {36} \) and thus must have a functioning embryo-trophoblast unit. To also support this concept, Johnson et al.\(^ {45} \) postulate that the embryo (apart from the trophoblast) plays an essential role in inducing the production of progesterone by the ovary which is superimposed on the luteotrophic effect of \( \beta \)-HCG from the trophoblast. Kada et al.\(^ {46} \) studied \( \beta \)-HCG levels in early pregnancy in order to find if the slope of the log of \( \beta \)-HCG concentrations over time can distinguish between normal intrauterine pregnancies, ectopic pregnancies and spontaneous abortions. The slope of the logarithm of \( \beta \)-HCG of all normal pregnancies was greater >0.05 (25% increase over 2 days), and 42% of ectopic pregnancies have slopes below this level. Stewart et al.\(^ {47} \) performed a similar type of study, all of their normal intra-uterine pregnancies had slopes above 0.10% (60% rise over two days), and 57% of ectopic pregnancies have slopes below this level. In essence, ectopic pregnancies that have a living embryo present, behave similarly in biochemical terms to normal intra-uterine pregnancies. Ectopic pregnancies that had embryonic death occur, act biochemically similar to spontaneous abortions. The progesterone level of <5 ng/ml (instead of 9.4 ng/ml) and a \( \beta \)-HCG increase less than 25% over two days (instead of 60%) were used here because this errs on the side of caution. This criterion excludes those ectopic pregnancies in which embryonic life is still possible.

This again is not a stand-alone criterion; this is only useful when the clinical information makes the diagnosis of ectopic pregnancy very likely. Also, the diagnosis of embryonic death may be made with criteria other than the one listed above. A conscientious physician may diagnose embryonic death with the available clinical information of the particular patient, but this would need to be done on a case-by-case basis. Individual physicians and hospitals may vary with regard to the reliability of the diagnostic tests just stated.

Third, let us consider the case where it is uncertain whether embryonic life or death is present. When the clinical information cannot determine that embryonic death has occurred, waiting and further diagnostic studies would be indicated. If there is doubt whether embryonic death has occurred, then it should be assumed that embryonic life is still present.
The treatment options for ectopic pregnancy should be based on the presence or absence of embryonic life. If embryonic life is present, total salpingectomy or partial salpingectomy with tubal re-anastomosis are the only licit options available. Salpingectomy (partial or total) would be permissible using the principle of double-effect, and probably makes the most sense surgically as well. The growth of an ectopic pregnancy with embryonic cardiac activity probably causes a much more substantial degree of tubal damage as compared with an anembryonic ectopic, so tubal integrity is severely impaired and risk of future ectopic greatly increased. Salpingectomy in these cases would be the optimum treatment. Transplantation of the viable ectopic pregnancy into the uterus would be the best solution, but has had documented success only two times in the medical literature, as of this writing. The limited success of transplantation may be secondary to the lack of a living embryo present in the majority of ectopic pregnancies. If embryonic death is present, salpingectomy, salpingostomy, or methotrexate are all options for the patient, with the decision to be based on the clinical judgment of the physician. The growth of an ectopic with very early embryonic demise probably causes much less tubal damage as compared with a viable ectopic, so salpingostomy or methotrexate may prove to be adequate treatment options that also allow enhanced future fertility. In cases of doubt whether a living embryo is present, salpingectomy would be the only licit option available.

In conclusion, ectopic pregnancy is an unfortunate event that is increasing in frequency. In most cases of ectopic pregnancy, an embryo is not present. In cases where a living embryo is found or we are unable to determine if a living embryo is present, salpingectomy is the procedure to be performed. If embryonic death is diagnosed, then licit treatments are salpingectomy, salpingostomy, or methotrexate.

Transplantation of a living embryo into the uterus is the ideal procedure, and if perfected, would be a tremendous breakthrough in the treatment of ectopic pregnancy. Hopefully, success will come soon.

References


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