The Linacre Quarterly

Volume 70 | Number 3 Article 6

August 2003

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by

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This essay grew out of a presentation made to the medical staff of the hospital where I practice. I am a pathologist and claim no special expertise in the matter, however the topic of the morality of the use of methotrexate in an ectopic pregnancy is of concern to me because I am a physician and a Catholic. My institution is a secular one; I suspected that any attempt to present the moral issues surrounding methotrexate baldly was likely to fail. So I thought I'd approach the topic from a strictly medical perspective, do a brief review of the current literature, and see how methotrexate faired as a treatment alternative. Only after my "medical" presentation did I touch on the moral issues.

Ectopic pregnancies are common: they occur about once in every 150 pregnancies. The overwhelming majority — over 96% — occur somewhere within the Fallopian tube. The remainder are extratubal, implanting anywhere between the cervix and the interior of the abdomen. When an ectopic is diagnosed it represents a medical situation of the most serious nature. A few ectopics can be managed by close clinical follow up, as the mother's body will sometimes reasorb the pregnancy. However, the majority will require direct intervention. Even in those mothers who are being followed the physician must be capable of intervening at the first suggestion of an impending rupture, as a ruptured ectopic is a profound medical emergency with an extremely high mortality. There is no question, then, that the woman diagnosed with an ectopic pregnancy must be aggressively managed.

The traditional approach to management has been salpingectomy by laparotomy. Today the procedure is done via laparoscopy unless the patient is unstable (Kim & Fox, 1999), and has an essentially 100% cure rate (Gabbe 1996). The embryonic child is not destroyed directly in this procedure; she dies because she resides in the Fallopian tube which has been removed, and currently there is no way to keep her alive or reimplant her in the mother's womb. In complete (a.k.a. "radical") salpingectomy the entire tube is removed, leaving the remaining tube intact. In partial (a.k.a. "conservative" or "segmental resection") salpingectomy the segment of the tube containing the embryo is removed, and the remaining sections of the tube are re-anastomosed. In both procedures, the mother does retain fertility to a very high degree, as she has a remaining tube. Only in the instance where the affected tube is completely removed and the other tube has been previously damaged or removed is the mother's future fertility significantly impaired by the salpingectomy procedure. Regardless of the variant used, salpingectomy remains the "gold standard" of safety and efficacy against which all other procedures are compared. Further, the Church has long held that the procedure is morally acceptable (ERD 1971, no. 16; ERD 1994, no. 48). So, a treatment exists which is safe, highly effective, and can be done with all the benefits of laparoscopic surgery. Indeed, it is the standard against which all competing procedures are compared. Finally, it is morally acceptable.

Recent Developments

Over the past two decades or so, a number of other surgical approaches have been developed, including linear salpingotomy, salpingostomy, fimbrial evacuation, and related variants. They are known as "conservative procedures" because they have the common property of being "tube sparing" meaning that the embryo is dissected or suctioned out, usually through a small hole or linear incision. The tube is left largely intact. The hypothetical benefit is the possibility of better future fertility than in salpingectomy. These conservative procedures are safe, reasonably effective, and represent standard therapeutic alternatives to traditional salpingectomy in the U.S. However, though advertised as "better" than salpingectomy because they impair future fertility less, the benefits appear minuscule. If both tubes were present prior to the ectopic, there is essentially no difference between salpingectomy and conservative procedures in the likelihood of future intrauterine pregnancies. If there was only one tube prior to the ectopic, there *may be* a slightly higher chance of future intrauterine pregnancy after the tube sparing procedure than there would be after a traditional salpingectomy, but there is also a higher chance

of *future* ectopic pregnancy (Kim & Fox,1999) due to scarring of the tube. A very negative aspect of the conservative procedures is that they may be unsuccessful in removing all the trophoblastic tissue, and the persistent tissue then causes rupture and hemorrhage. For this reason, serial serum quantitative β-HCGs must be followed after these procedures until they decline to zero (this is true of salpingectomy as well) to ensure that there is no residual viable trophoblastic tissue. The risk of persistent trophoblastic tissue in the conservative procedures is between 3 and 17% (Kim & Fox 1999); this plus all other postoperative complications may be over 20% (Gabbe 1996, Vermesh et al, 1989; Sefer et al, 1990). Thus, while this essay is not primarily concerned with the conservative procedures, most of the medical (and moral) issues which apply to methotrexate apply to these procedures as well.

Methotrexate is a folic acid antagonist. Folic acid is necessary in the synthesis of DNA and thus methotrexate effectively hinders rapidly growing tissue by interfering with replicate DNA replication. Although it now has numerous uses, methotrexate's first, and possibly still most successful use is in the chemotherapeutic treatment of childhood leukemias and lymphomas. Indeed, this is one of the miracles of modern medicine: childhood leukemia was a death sentence until the introduction of methotrexate. Now, it is a survivable disease, and children are alive and well today who would have been dead for years but for the use of this drug. Another cancer which methotrexate successfully treats is choriocarcinoma, a malignancy of trophoblastic cells.

At around three to four days into the life of the embryonic child, when she is at the "morula" (mulberry) stage, she divides into an "inner cell mass" and an "outer cell mass". The inner mass will develop into the embryo and fetus; the outer mass will develop into the trophoblast and, eventually, the placenta. This division happens before she implants; indeed it's a necessary thing for her to do as she is sailing down the Fallopian tube to the womb, looking for a place to alight for the next few months. It's sort of like an airplane lowering its landing gear while on final approach, with the runway well in sight. The embryonic child lowers her trophoblasts in preparation for landing. Well, anyway, trophoblasts can become neoplastic. When they do so they usually develop as choriocarcinoma, a highly malignant and fatal cancer. Many choriocarcinomas are in no way associated with a pregnancy; they originate in the ovary as a primary germ cell tumor. In those choriocarcinomas that are related with a pregnancy the pregnancy was rarely normal; the malignancy arises after a spontaneous miscarriage. Only one out of 150,000 or more normal term pregnancies result in choriocarcinoma. Regardless, trophoblasts (be they normal or abnormal) are exquisitely sensitive to the effects of methotrexate, and that is why

methotrexate turned this universally fatal malignancy into one which is highly curable with an excellent long term prognosis.

Some twenty years ago, methotrexate began to be used in the treatment of ectopic pregnancies. The rationale came out of its success in the treatment of choriocarcinoma: by destroying the trophoblast of an ectopic pregnancy, it might be successful in inducing a tubal abortion. Since its initial trials methotrexate has become widely available in U.S. hospitals as an alternative to surgery in select patients. It offers the potential benefits of avoidance of surgery, maintenance of fertility, and reduced costs. Not all women with ectopic pregnancies can be treated with methotrexate; the American College of Obstetrics and Gynecology has published guidelines indicating which patients are candidates (ACOG Practice Bulletin No. 3, 1998). Some controversy exists regarding these guidelines (Lipscomb, 1999; Barnhart et al, 2000; Lipscomb et al, 1998). Regardless, recent estimates are that 30-40% of women with ectopic pregnancies would be eligible for methotrexate therapy (Barnhart et al, 2000).

Two Regimens Most Common

Many methotrexate regimens have been used in the treatment of ectopic pregnancy. The two which seem to have emerged as the most commonly used are the "single intramuscular dose" regimen (where repeat IM doses are given only if the serum β-HCG doesn't fall by a specified amount within a specified time) and the "multidose regimen" (where four scheduled doses are given, and then repeated if necessary). Success rates for these regimens vary considerably. Many studies report success rates of 80-90%, generally about the same as the conservative surgical procedures (Lipscomb et al, 1998; Keefe, 1998; Hajenius, 1997; Stovall & Ling, 1993; Stovall et al, 1991). However, other authors report considerably poorer outcomes, in the range of 65% (Stika et al, 1996). With the "single dose" regimen, so many women require repeat doses that the term "single dose" has been called "a misnomer" (Barnhart et al, 2000) and "not effective enough in eliminating tubal pregnancy..." (Hajenius, 2000). Some argue that methotrexate shouldn't be used alone at all, but only in combination with other abortifacients (Perdu et al, 1998). This is significant insofar as many practitioners currently consider the single dose regimen to be the method of choice. In addition, an ectopic pregnancy is not considered resolved until the serum quantitative β-HCG declines to zero due to the possibility of residual trophoblastic tissue, as discussed above. With methotrexate, the period of time that the patient must be followed with serial blood draws and measurements is considerable longer than any of

the surgical techniques, averaging 35 days post treatment and sometimes taking up to seven weeks (Barnhart et al, 2000).

Abdominal pain following methotrexate therapy is a significant issue, occurring in over half of patients (Carr and Evans, 2000; Stika et al, 1996). Some practitioners seem to feel that the pain is a consequence of the prolonged tubal abortion which the drug is inducing. Regardless of the cause, the continuing pain drives follow up evaluations that sometimes become in themselves quite significant. Indeed, the need for a surgical procedure to evaluate the persistent pain following methotrexate therapy has been reported to be as high as 22% (Stika et al, 1996). Methotrexate therapy, especially in the single dose regimen, is theoretically cheaper than a surgical treatment: that is, in fact, one of the "selling points". There is some data to support this (Morlock, 2000). However, when prolonged follow up, need for repeat dosing, not-infrequent need for surgical intervention, and time lost from work is all factored in methotrexate may not be cheaper, and may even be more expensive, than conservative surgical procedures (Mol, 1999).

Another "selling point" of methotrexate therapy has been that the prospects for future fertility are better than after surgical therapies. But future fertility after treatment of an ectopic pregnancy seems to be no worse than, but no better than, conservative surgical procedures (Keefe, 1998; Debby, 2000; Barnhart, 2000; Carr and Evans, 2000; Hajenius, 2000; Hajenius, 1997).

Extratubal ectopic pregnancies are rare, at 3-4% of all ectopics (Kim and Fox, 1999). When they occur, however, they can require extensive surgical procedures with potential significant morbidity, and which may leave the woman sterile. Because of this, methotrexate treatment has been held out as a valuable alternative procedure that can prevent the need for extensive surgery. Although some authors consider methotrexate a first line therapy in such an instance, the same authors note that "the success rate of medical management is not truly known... Most likely, it is substantially lower than the success rate of primary treatment of a tubal gestation." (Barnhart et al, 2000). Other authors state that "it is difficult to make general recommendations" concerning methotrexate versus surgical management of such patients due to the small numbers (Kim and Fox, 1999). At least one paper recommends "extreme caution" in the use of single dose methotrexate in a specific type of extratubal ectopic, an interstitial pregnancy (Gherman, 2000).

In summary, there is a great deal of enthusiasm in the obstetrical literature concerning the use of methotrexate in ectopic pregnancy. One wonders why, insofar as it seems to be, at best, a mediocre treatment alternative: "...No clear evidence favors methotrexate or salpingostomy as

the treatment of choice. Successful treatment rates are nearly identical among the two potions, as are rates of subsequent fertility..." (Carr and Evans, 2000).

The moral issues have been thoroughly covered elsewhere (May, 2000). Salpingectomy does not constitute a direct abortion because it does not kill the child directly. Indeed, the intent is not to kill the child. The intent, as mentioned above, is to remove the portion of tube in which the child resides. The child dies as a tragic but unintended and unavoidable consequence. Controversy among moral theologians about the use of methotrexate seems to revolve around whether destruction of the trophoblast by the drug constitutes a direct abortion, with at least some authors concluding that it does not (Clark, 2000). The idea is that the trophoblast is not the part of the embryo that develops into the fetus (the "inner cell mass" mentioned above), but the part that develops into the placenta (the "outer cell mass"). Therefore, if I follow the reasoning, since the drug doesn't kill the embryo directly, just her landing gear, it is not a *direct* abortion and is OK from a moral standpoint for use in the treatment of the ectopic pregnancy. Perhaps. But it is worth noting that the *obstetrical* literature unabashedly and unreservedly refers to the procedure as a tubal *abortion* of the embryo, and the obstetrician authors don't seem to give it a second thought. Indeed, methotrexate is frequently used in combination with misoprostol for, well, routine elective *abortions* of intrauterine pregnancies of less than 49 days' duration (Creinin, 2000; Pymay & Creinin, 2000; Creinin 1998; Creinin, 1997). Interestingly, another folic acid antagonist, which presumably worked via the same mechanism as methotrexate, was used in the 1950s specifically to induce therapeutic *abortions* in first trimester patients (Creinin, 2000). It is also worth keeping in mind that the intrauterine device, and, sometimes, injectable/implantable hormones and birth control pills, do not kill the embryo directly; they create a hostile environment within the womb which impedes successful implantation. In this context, though, they are often considered abortifacients. Indeed, the *abortion pill*, mifepristone, doesn't kill the embryo, or affect her directly in any way. It merely blocks the effects of progesterone on the uterus, effects which the uterus needs to support the embryo. Without progesterone, the uterus cannot support the embryonic baby, and expels her (Creinin, 2000; Pymar & Creinin, 2000; Schatz et al, 1997). So, to suggest that methotrexate is not an abortifacient because it only destroys the trophoblast, and not the "embryo proper" (if, indeed, such a distinction can be legitimately made; I don't accept it) seems to be splitting hairs just a little too fine. I believe that the reason the obstetrical authors don't trouble themselves as to whether these various drugs and devices cause direct abortions is because they know full well that the *intent* is to cause an abortion. Never mind the mechanism. To my

untrained and admittedly unsophisticated mind, use of methotrexate can't seem to reasonably be anything other than the intended direct abortion of the implanted embryo as the means of treating the ectopic pregnancy.

Because I believe methotrexate to represent a direct abortion of the embryo, and because the *Catechism of the Catholic Church* teaches that direct, intended abortion is never morally acceptable (CCC #2270, 2271), the use of methotrexate to treat an ectopic pregnancy would not seem morally admissible. This is because (as the Catechism further teaches) a good end — saving the mother's life — may not be obtained by an evil means — the abortion of the embryonic child (CCC, #1756). Further, as the Church has long held, there is a safe and highly effective procedure available which is morally acceptable in the form of salpingectomy. Indeed, salpingectomy is more effective than methotrexate. Thus, methotrexate as a therapeutic alternative in the treatment of ectopic pregnancy would seem inadmissible to me, a Catholic physician, on moral grounds. Despite the continuing enthusiasm for the procedure in the secular literature, it should seem highly questionable to any physician on medical grounds.

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