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The controversial pathophysiology of tubal pregnancy

La controversia sobre la fisiopatología del embarazo tubario

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Ectopic pregnancy plagues a large number of women of reproductive age and is one of the leading causes of maternal mortality and morbidity. The incidence of ectopic pregnancy has been steadily rising over the past two decades, reaching epidemic proportions in most industrialized countries. The reasons for this epidemic are poorly understood although changing trends of some known risk factors have been observed and could, in part, account for the rising incidence. The increasing popularity of conservative tubal surgery and ovulation induction drugs have been implicated, but the evidence is inconclusive. The multiplicity of theories on the etiology and pathogenesis of ectopic pregnancy, as well as the controversies they raise, reflects our lack of fundamental knowledge of the factors that regulate tubal function and the development and implantation of the early human embryo.

INTRODUCTION

In a surveillance summary by the Centers for Disease Control (CDC), it was reported that, in 1986, 73,700 pregnant women, 1.4 percent of all pregnancies, were hospitalized for ectopic pregnancy in the USA (1). The case fatality rate was 4.9 per ten thousand, 13 percent of all reported maternal deaths, making ectopic pregnancy the second leading cause of maternal death after hypertensive disorders of pregnancy. The CDC also reported a rising rate of ectopic pregnancy, from a low of 4.5 per thousand in 1970 to a high of 15.2 and 14.3 per thousand in 1985 and 1986 respectively. Higher rates have recently been reported from Finland and similar trends have been observed in other industrialized countries (2-4). It has been suggested that the actual incidence of ectopic pregnancy may be even higher since it is estimated that 10-50 percent of ectopics go unrecognized (5). Accumulated epidemiologic knowledge of ectopic pregnancy indicates that pelvic inflammatory disease and tubal surgery seem to bear the strongest association to ectopic pregnancy (6-8). In fact, those factors along with a history of infertility were confirmed as independent risk factors for ectopic gestation (9). Although the reasons behind the sharp epidemic of ectopic pregnancies worldwide are not fully understood, the rising incidence of PID over the past two decades has been implicated (10). In a study from Finland, which has the highest ectopic rate in the world, an increased incidence of PID was observed in recent years (11). The authors concluded, however, that such changing risk factor trends could not alone account for the observed threefold increase in the rate of ectopic pregnancy. Other changing trends that have been also implicated include: 1) the increased popularity of conservative tubal surgery, 2) the widespread use of fertility drugs, 3) the declining use of the combined oral contraceptive pill in favor of other forms of contraception, 4) a tendency to postpone childbearing into later years (12), and 5) improved diagnostic capabilities that allow detection of early ectopics that might have resolved spontaneously and gone unnoticed otherwise (13).

THE ROLE OF PELVIC INFLAMMATORY DISEASE (PID) AND THE INTRAUTERINE DEVICE (IUD)

Significant controversy surrounds the role of the IUD in ectopic pregnancy. A higher

predisposition of PID among IUD users is widely believed to underly their increased risk for ectopic gestation (14). This increased risk, however, is not uniform for all types of IUD's and for all patient populations. Education levels, smoking history, parity and the number of sexual partners have been noted to be confounding variables in the association between IUD use and ectopic pregnancy (15). In recent controlled studies, the copper containing IUD has been singled out as having a much lower associated risk of ectopic pregnancy when compared to inert and steroid containing IUD's (15, 16). In a histologic study of endometrial biopsies after years of copper IUD usage, a striking absence of inflammatory changes was noted (17). It has also been suggested that copper ions, in concentrations released by the copper IUD, can significantly inhibit chlamydial growth in human endometrial cell cultures (18). Although these findings suggest that copper may have bacteriostatic and anti-inflammatory effects, it is not known whether those are the mechanisms responsible for the lower risks associated with the use of copper IUD's or whether copper effects on gametes and fertilization are involved. Although seemingly plausible, infection as an underlying cause for the association between IUD use and ectopic pregnancy remains controversial. The one central issue in this controversy is the mechanism by which infection predisposes to ectopic implantation. Although the mechanical sequelae of salpingitis (adhesions and epithelial damage) are thought to predispose to ectopic implantation by impeding tubal transport, several studies have challenged this concept. In Finland, where IUD use is prevalent, pelvic adhesions were noted less frequently among IUD users with ectopic pregnancies than among non-users with ectopics (11). Moreover, two histologic studies have shown a lack of consistent association between ectopic pregnancy and evidence of tubal infection or inflammation (19, 20). In fact, such evidence was lacking in 70% and 50% of the cases respectively. These findings suggest that there may be more to the association of PID and ectopic pregnancy than mechanical tubal factors. Other yet unexplored alterations in uterine and tubal physiology may be associated with PID and may be contributing to the genesis of ectopic pregnancy.

THE ROLE OF SPECIFIC TUBAL FACTORS

Ectopic pregnancy seems to be mostly an affliction of humans. Hodgen observed only three tubal pregnancies among 3,000 primates during 15 years of experimentation (21). In lower mammalian species, several investigators have noted that early embryos fail to develop and implant if mechanically locked in the oviduct, while implantation and development could be easily promoted in other tissues (22-24). In fact, this phenomenon accounts for the lack of an animal model of tubal pregnancy. In a recent study by Pauerstein *et al.*, in which patches of rabbit endosalpinx were grafted on the rabbit endometrium, implantation occurred on the endometrium, but not on the grafted endosalpinx (25). Although it is not clear whether this represents a specific tubal effect or a nonespecific effect of grafting, it is postulated that the rabbit endosalpinx elaborates specific factors that inhibit early development and/or implantation. Further studies are needed to determine the nature of such factors in mammalian oviducts if they truly exist. It is of more than academic interest to investigate the presence of similar factors in the human oviduct and to determine whether disease processes (e.g., infection) or hormonal factors (*e.g.*, estrogen to progesterone ratios) affect their expression.

THE ROLE OF TUBAL SURGERY

Iatrogenic causes that have been implicated in the recently observed trends in ectopic pregnancy include the increased use of ovulation drugs and the increased popularity of conservative tubal surgery for a host of indications (25, 26). The use of conservative tubal surgery for the treatment of infertility of various etiologies (endometriosis, proximal and distal tubal obstruction, adhesions, etc.) as well as for

treatment of ectopics (salpingostomy, salpingotomy and segmental resection) has increased in recent years, raising concerns as to whether this is contributing to the rising rates of ectopic pregnancy. Although recent epidemiologic evidence suggests that tubal surgery is an independent risk factor in ectopic pregnancy (9), the numbers are small and it is not clear as to whether all types of tubal surgery are implicated. A history of tubal surgery among patients with ectopic pregnancies is rarely the only variable and more often than not multiple risk factores coexist. In addition, the more intense surveillance in this group of women may result in the diagnosis of greater numbers of early ectopics that are destined to resolve spontaneously, leading to an apparently higher ectopic rate (28). Of particular interest is the high recurrence rate of ectopic pregnancy estimated at 10-20 percent (29), and whether conservative surgery in ectopic pregnancy accentuates this rate. This issue has triggered controversy over what modality of surgery is most appropriate to decrease or prevent recurrences. Based on histologic observations of patterns of trophoblastic spread, De Cherney *et al.*, recommended segmental resection of the isthmic ectopic as the treatment of choice (30), whereas Smith *et al.*, had a contrary opinion (31). Recurrences after conservative treatment of ectopic occur on the contralateral side in 50 percent of cases (2). This suggests that an underlying tubal dysfunctional state, which is often bilateral, is a more likely cause for the recurrence than the previous tubal surgery per se. Moreover, a histologic study of 15 tubes with recurrent ectopics after previous conservative surgery revealed that the recurrence could be related to the sequelae of previous surgery in three cases only (32). In the remaining cases, the previous surgical scar was well healed with no evidence of stenosis or adhesions and underlying diffuse tubal pathology seemed to be the major contributing factor.

THE ROLE OF ADVANCED REPRODUCTIVE TECHNOLOGY AND FERTILITY DRUGS

Unexpectedly high rates of ectopic pregnancy have been reported after ovulation induction and an association has been made between high periovulatory estrogen levels and ectopic pregnancy (33, 34). It is, however, difficult to determine whether this is a purely hormonal effect or whether confounding variables are partially responsible. Women receiving fertility drugs tend to have other risk factors for ectopic pregnancy (age, history of infertility, and history of tubal surgery among others). In a study of 230 women with menstrual abnormalities only (negative laparoscopy, negative hysterosalpingogram and no history of PID) who were treated with human pituitary gonadotropins, a 2.9 percent ectopic rate was observed (35). Earlier studies by another group using human menopausal gonadotropins found no such heightened risks (36). The explanation given by the authors for this discrepancy was based on the difference in LH/FSH ratio between pituitary and menopausal gonadotropins. They suggested that a higher LH/FSH ratio in pituitary gonadotropins could have resulted in a suboptimal estrogen to progesterone ratio that, in turn, is conducive to ectopic implantation. A similar situation has been claimed to occur after discontinuation of the oral contraceptive pill. A short lived rebound in gonadotropins with an elevated LH/FSH ratio is thought to underly a higher incidence of ectopic pregnancy during this period (37). Other associations where an underlying hormonal basis for ectopic pregnancy is likely include the minipill and the progesterone medicated IUD (4, 38-40). An ectopic rate of 10 percent was observed among failures of postcoital diethylstilbestrol (DES) contraception (41). Further evidence relating hormonal factors to ectopic pregnancy comes from anecdotal case reports of ectopic pregnancies occurring after inadvertent luteal phase administration of GnRH agonists (42, 43). It has been suggested that the "flare-up" of gonadotropins after GnRH administration is parallelled by a flare up of progesterone which may alter tubal motility (44). In fact, studies have shown that electrical, mechanical and morphological properties of the human fallopian tube are modulated by progesterone (45-47). It seems plausible that an altered estrogen to progesterone

ratio would result in aberrant ciliary function and muscular contractility of the fallopian tube. Should this occur during transport of gametes and embyos, it could readily predispose to ectopic implantation.

CORPUS LUTEUM FUNCTION AND ECTOPIC PREGNANCY

The corpus luteum, being the organ that maintains the hormonal milieu of early gestation, has been a subject of several studies to evaluate its role in ectopic gestation. In a study of 67 ectopic pregnancies, the corpus luteum was identified on the contralateral ovary in 28 percent of cases (48). Other retrospective studies have similarly reported a high incidence of contralateral corpora lutea in ectopic pregnancies (49, 52). It has been suggested that this could happen as a result of either reflux of an embryo that has entered the uterine cavity into the contralateral tube, or peritoneal transmigration of the oocyte or embryo to the other side (19). The significance of this observation is not clear, however, since no information on the incidence of transmigration in normal pregnancies is available. Moreover, in a study of 114 ectopic pregnancies, no significant association was found between individual risk factors for ectopic pregnancy and the position of the corpus luteum (52). Perhaps of greater significance is the endocrine function of the corpus luteum in ectopic gestations. This has been the subject of several studies (53-55). In most such studies, a significantly lower luteal serum progesterone was observed in ectopic pregnancies as compared to normal controls. Whether this represents a primary corpus luteum defect, or one that is secondary to suboptimal production of HCG and other hormones by unhealthy ectopic trophoblasts is controversial. Although it is currently believed that ectopic pregnancies exhibit lower hCG levels and lower rates of hCG rise than normal pregnancies of comparable gestational ages (46), there has been suggestions that lower serum progesterone in ectopic pregnancies is not due to subnormal hCG production (54). Norman *et al.*, using a case of control design at eight weeks of gestation, showed comparable immunoreactive and bioactive hCG levels in normal and ectopic gestations with significantly lower steroid levels in the latter group (56). Sauer *et al.*, found that in spite of maintained hCG levels, serum sex steroids decline in spontaneously resolving ectopic pregnancies (57). It has also been noted that a corpus luteum cannot be visually or sonographically identified in 14-33 percent of ectopic pregnancies (53, 58). Taken collectively, these studies may suggest a primary corpus luteum defect as an underlying factor in the genesis of some cases of ectopic pregnancy. Such a suggestion is in line with the evidence for a hormonal basis of ectopic pregnancy. It should be remembered, however, that trophoblastic or embryonic signals other than hCG may be needed for normal corpus luteum steroidogenesis and that corpus luteum defects in ectopic pregnancy may still be secondary to abnormalities of those signals. It is unlikely that this issue will be resolved until our fundamental knowledge of corpus luteum function and the factors that regulate it in normal and ectopic pregnancy is expanded.

CONCLUSIONS

Recent advances in early diagnosis and management of ectopic pregnancy have significantly reduced the mortality and morbidity rates associated with this affliction in the developed world. On the other hand, the incidence of ectopic pregnancy continues to rise and has truly reached epidemic proportions and the consequences of tubal pregnancy in less developed countries are devastating. At present, fundamental knowledge of etiology and pathogenesis of ectopic gestation is lacking. Current theories of pathogenesis are diverse and controversial and are based mainly on epidemiologic evidence. A better knowledge of early embryonic development and implantation as well as the endogenous and exogenous factors that regulate them is needed if we are to gain insight into the processes that lead to ectopic gestation.

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