Tubal ectopic pregnancy: a patho-physiological explanation involving endometriosis

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The condition of tubal ectopic pregnancy is presented from diverse points of view, bringing out physiological explanations for its occurrence in primates and striking absence in other mammals. Part of the flexibility underlying ectopic pregnancy in humans stems from the absence of a uterine luteolytic mechanism, enabling early embryonic development in the Fallopian tube without compromising function of the corpus luteum. Attention is devoted to a potential overlap between the composition of tubal and uterine fluids, and to specific mixing between the two fluid compartments, expressed in an ability of the human oocyte or zygote to tolerate transplantation to the uterus. Perturbed tubal oocyte transport is seen as a contributory factor, not least as a sequel to episodes of infection and a modified endosalpinx, but the essay then reasons strongly for an involvement of endometriosis in the aetiology of tubal ectopic pregnancy. Proliferation of refluxed endometrial tissue arrested within the Fallopian tube could provide the epithelial characteristics of a uterine environment. Accordingly, an experimental model is proposed for tubal ectopic pregnancy in animals based upon transplants of endometrial tissue and the subsequent introduction of embryos into both the Fallopian tubes and uterus; the latter would suppress the luteolytic mechanism. Finally, advances are suggested based upon molecular scanning of human ectopic tissues and those derived from animal models. If molecular probes could be developed to detect either early tubal pregnancy or a propensity to this pathology, such advances would clearly have clinical relevance—not least in view of an enhanced incidence of tubal pregnancy arising after assisted reproduction technology.

Key words: assisted reproductive technologies/ectopic pregnancy/endometrial transplants/endometriosis/Fallopian tube

Introduction

Putting to one side the occasional bizarre or exceptional claim, tubal ectopic pregnancies would appear to be restricted to primates (Figure 1). This pathological condition does not occur in laboratory rodents or domestic farm animals, nor has a model for tubal pregnancy been demonstrated by arrest of embryos in the Fallopian tubes using appropriately positioned ligatures. Such artificially-retained embryos may progress to the blastocyst stage in the Fallopian tube, but development thereafter is severely compromised and degeneration soon follows (Murray et al., 1971). Even if this were not so, a tubal pregnancy would not become established since the presence of one or more embryos is required in the uterus to prevent activation of the luteolytic mechanism that causes demise of the corpus luteum or corpora lutea: this mechanism involves an oxytocin-prompted secretion of uterine prostaglandin (PG)F_2α (Niswender et al., 2000). Here again, the primate is an exception, for even if an embryo is arrested in the Fallopian tube and unable to exert a direct influence on the endometrium, a uterine luteolytic mechanism is not set in train. Primate ovarian tissues seemingly act to regulate their own luteal lifespan during the menstrual cycle, initiating their own oxytocin–PG lytic loop, necessary gene activity being regulated by the interplay of progesterone and estradiol-17β. Thus, in the absence of embryonic anti-luteolytic activity derived from the uterus, the stage is set for the possibility of a tubal ectopic pregnancy in primates (Levasseur, 1983; Hunter, 1988). What other factors require consideration?

Anomalous tubal transport

Clearly, some means of impeding passage or specifically arresting movement of a developing embryo would be needed during progression along the Fallopian tube. Such wayward transport could involve abnormal ciliary function and/or spasm in the myosalpinx, especially in the layer of circular muscle, arising from either local endocrine perturbations or those associated with emotional disturbances or more profound psychosomatic disorders. Inadequate development of the corpus luteum and inappropriate secretion of progesterone may
be sufficient to disrupt normal passage of an embryo into the uterus (Hunter, 1988). An alternative possibility is that the Fallopian tube has a congenital abnormality or has become partially or largely obstructed, sufficiently so to arrest an oocyte or embryo even if not a spermatozoon: the relative dimensions can be considered as ∼100 µm for the diameter of an oocyte and 5–8 µm for the sperm head.

Viewed conventionally, loss of tubal patency would be a sequel to one or more episodes of infection arising, for example, from Chlamydia trachomatis (Henry-Suchet and Loffredo, 1980; Sweet, 1982; Brunham et al., 1985; Tuffrey et al., 1986). Gonococcal and tuberculous infection may also be involved in such pelvic inflammatory disease, and complications can arise at a tubal level following septic abortions. Scarring and subsequent occlusion of the Fallopian tube tend to be frequent sequelae to inflammation arising from bacterial infection. Even if patency had not been seriously compromised by infection, the endosalpinx would have been damaged and its surface modified during one or more episodes of salpingitis. The condition of the ciliated epithelium should certainly be questioned. At a biochemical level the epithelium may no longer present molecular markers representative of a Fallopian tube.

As to the site of tubal ectopic pregnancies, implantation usually favours the mid-portion of the Fallopian tube, but has also been noted in both the proximal (cranial) ampulla and interstitial region. In a series reported from Jamaica, the distribution was 7% on the fimbriated infundibulum, 42% in the ampulla, 28% in the isthmus and 13% interstitial, with the remainder being imprecisely determined (Douglas, 1963). Diverse Fallopian tube sites have also been noted in monkeys (Benirschke, 1969).

**Role of luminal fluids**

At this point, it is instructive to return to lessons learnt from laboratory and domestic farm animals. Prior to the stage of organized endometrial contact and attachment that herald the onset of implantation, the embryo depends for metabolic support upon (i) its own cytoplasmic reserves of nutrients originating in the oocyte and diminishing with time and developmental stage, and (ii) components of the Fallopian tube luminal fluid and—in due course—uterine fluid, notably pyruvate, lactate and glucose (Brinster, 1965, 1973; Biggers et al., 1967; Leese, 1988; Tay et al., 1997). A critical finding concerning such fluids is that they are of characteristic composition but nonetheless change with the stage of estrous cycle as regulated by the ratio and concentration of ovarian steroid hormones and in step with the embryo’s own metabolic requirements. In addition, but following from the previous point, the fluids differ between Fallopian tube and uterus, such a distinction being maintained by a formidable utero–tubal junction (Andersen, 1928; Lee, 1928; Fléchon and Hunter, 1981) and initially also by viscous glycoprotein secretions that accumulate in the caudal portion of the isthmus. The fluids also differ in composition according to region along and within the Fallopian tube (Roblero et al., 1976; Leese, 1988; Nichol et al., 1992). This last point is perhaps surprising, bearing in mind the influence of myosalpingeal contractions and cilia beat, but mechanisms have apparently developed to stabilize such regional or micro-environments. Possible mechanisms might involve the complex epithelial architecture of ridges, folds and grooves (Yániz et al., 2000) and the distribution of macromolecules including specific glycoproteins (Hunter, 1994). In fact, these points concerning specialized tubal and uterine fluids provide additional explanations as to why initiation of tubal ectopic pregnancies would be highly improbable in laboratory or domestic farm animals.

What bearing do these various points have on the physiology of early embryonic development in primates? The very occurrence of tubal ectopic pregnancies would suggest some flexibility in the provision of—or requirement for—substrate in the tubal luminal fluid. It could perhaps be argued that the substrate...
requirements of primate embryos are less stringent than those of laboratory rodents or, more plausibly, that there is a considerable overlap in the composition of luminal fluid in primates between the Fallopian tubes and uterus. Bearing in mind the nature of the tubo-uterine interface within the intramural portion of the tube and the lack of swollen polypoid processes at the actual junction (Lee, 1928; Patek, 1974), the latter seems a strong possibility. Tubal fluids would enter the uterus and vice-versa, mixing would occur, and their compositions would no longer be unique, even if they were so at the time of their formation. Not only does the existence of tubal ectopic pregnancy support these views, but the fact that gametes can be introduced directly into the uterus and generate a pregnancy emphasizes the ability of the zygote and developing embryo to tolerate such fluids (Hunter, 1977, 1998). The result of Estes’ operation, transplantation of an ovary into the uterus in patients with blocked Fallopian tubes (Estes, 1924; Estes and Heitmeyer, 1934), when followed by pregnancy, would lead to a similar conclusion. In reality, both flexibility in the embryo’s substrate requirements and overlap in the composition of tubal and uterine fluids could underlie the occurrence of ectopic pregnancy. Indeed, development of an ectopic pregnancy at diverse sites within the abdomen clearly demonstrates tolerance in the initial fluid environment of the human embryo.

Ectopic pregnancy adequately explained?

In conjunction with the earlier remarks concerning regulation of the corpus luteum lifespan, the proposals in the previous paragraph may be sufficient to account for the existence of tubal ectopic pregnancy. Bearing in mind a surprisingly high incidence of this condition following transcervical passage of a catheter and introduction of human embryos directly into the uterus in fertility clinics (Maymon and Shulman, 1996)—primarily a reflection on physical aspects of the transplantation procedure and consequent myometrial activity, but perhaps also an indication of modified tubal physiology (Hunter, 1988, 1998)—an explanation for the susceptibility of primates to this pathological condition need go no further. However, there is one other aspect worthy of serious consideration and it appears to have received little systematic attention, at least on the printed page; it concerns a putative involvement of endometriosis.

Involvement of endometriosis

In this pathology, endometrial tissue shed during menstrual contractions is displaced in a retrograde manner through the Fallopian tubes into the peritoneal cavity (Benirschke, 1969; Oral et al., 1996), there to attach to the surface of abdominal organs covered with visceral peritoneum. In such sites, the tissue (glands and stroma) may (i) prolife rate, (ii) respond in a cyclical manner to ovarian steroid hormones, and (iii) cause episodes of discomfort or pain to a lesser or greater degree. These points represent the current dogma. What appears not to have been sufficiently considered is the extent to which fragments of refluxed endometrial tissue may be arrested within a Fallopian tube to generate a region possessing uterine characteristics. This could conceivably occur spontaneously in a healthy tube under an inappropriate pattern of contractile activity or with a degree of stasis associated with stress. More probably, arrest of an endometrial tissue fragment would have occurred in a Fallopian tube whose epithelium had been damaged and patency perhaps compromised by a previous history of disease. Such an endometrial fragment could show a marked phase of angiogenesis and would respond to the cyclical secretion of estradiol and progesterone in a tubal site; indeed it might hyper-respond in a locally privileged manner and proliferate actively. This would be a reflection of locally-elevated concentrations of ovarian steroid hormones reaching the vascular arcade of the Fallopian tube via a counter-current transfer system in the region of the plexus between the ovarian vein and tubal branch of the ovarian artery (Hunter et al., 1983; Einer-Jensen, 1988; Einer-Jensen and Hunter, 2000).

Whereas sperm might be able to progress within a Fallopian tube containing one or more endometrial fragments, the possibility of an oocyte or embryo descending such a tube would be much reduced—a point already made in terms of relative dimensions of spermatozoon and oocyte. Not only might an embryo be arrested or trapped in such a manner, but the fluid microenvironment of the pseudo-endometrial surface together with its specific molecular architecture might act to promote and sustain development and implantation of an embryo. In a phrase, an embryo might perceive components characteristic of a uterine milieu, albeit within the constraints of a tubal site, these facilitating and indeed encouraging the processes of attachment and implantation.

Although one could speculate on the nature of the endometrial molecules that might be involved in such a scenario, and which would modulate interactions with the highly invasive trophoblast (Edwards, 1980), it would be more instructive to examine clinical specimens at known stages of development. An approach to tubal pregnancy currently in favour involves laparoscopic-guided injection of methotrexate, PGF$_{2\alpha}$ or hypertonic glucose into the gravid Fallopian site to compromise the embryo and conserve the tube (Maymon and Shulman, 1996). However, there will also be clinical circumstances in which portions of tubal tissue and contents are removed from the patient during salpingostomy or salpingectomy. If such tissues could be subjected to rigorous modern analysis to establish the presence of endometrial marker molecules (proteins or mRNAs) interacting with chorionic tissue, then the present hypothesis would be strengthened (Campbell and Thomas, 2001). Overall, what has been argued in this section is that human uterine fluid and endometrial tissue can reflux into the Fallopian tube lumen or even abdomen, enabling a trapped or expelled embryo to continue development and implant in an ectopic site, even though the site may not be distinguished as such; in other words, it may present a ‘uterine-like’ environment (Hunter, 1998).

Development of an animal model

This line of study could be conducted in conjunction with— or preliminary to—development of an animal model. Endome-
triosis is not a feature of farm and laboratory animals, and previous attempts to develop non-primate models of extrauterine pregnancy have not met with success (Adams, 1977). A suitable model would involve grafting endometrial tissue into different regions of a single Fallopian tube, the contralateral tube remaining as an intact control in a polytocous (polyovular) species such as the rabbit. A suggestion would be that tissue grafting into the ampullary region or that of the ampullary–isthmic junction would be simpler and possibly more successful than attempted grafting into the more muscular and limiting isthmic portion of the tube. Pregnancies might be established spontaneously in animals bearing successful autotransplants or might require unilateral transfer of embryos by way of the fimbriated infundibulum into the ampullary portion of the tube above the region of the graft.

The value of developing such an animal model of tubal ectopic pregnancy would lie in its affording a means of systematic analysis of the molecular messages underlying and perhaps even prompting initiation of embryo–epithelial interactions in an extrauterine site (Campbell and Thomas, 2001). If the model could generate a tubal pregnancy with a predictable level of success, then molecular studies would be placed on a precise chronological footing. Such findings might in turn lead to simpler non-invasive treatments for relieving this life-threatening condition upon early detection and act to combat the reduction in fertility potential after current treatments. The primary objectives would be to develop an approach that (i) imposed minimum physical damage upon the Fallopian tube and (ii) reduced or negated the attractiveness of any remaining endometrial fragments to any future embryos in their vicinity. Ultimately, a means might be revealed of preventing attachment and establishment of refluxed endometrial fragments within the Fallopian tubes. Overall, a principal category of patients that comes to mind in the above context would be those undergoing treatment for infertility by means of assisted reproduction technology.

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References