ANIMAL MODEL OF HUMAN DISEASE

Diverticulosis and Salpingitis Isthmica Nodosa (SIN) of the Fallopian Tube

Estrogen-Induced Diverticulosis and SIN of the Mouse Oviduct

RETHA R. NEWBOLD, BILL C. BULLOCK, and JOHN A. McLACHLAN

From the Laboratory of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina; and the Department of Comparative Medicine, Bowman-Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Biologic Features

Since its description by Chiari in 1887, the etiology and pathogenesis of salpingitis isthmica nodosa (SIN) has been the subject of much debate. Although Chiari suggested that the lesion resulted from chronic salpingitis, more recent reports suggest SIN is a primary noninflammatory process similar to adenomyosis of the uterus[1] and diverticulosis of other organs,[2,3] although it is recognized that secondary infection may be a common occurrence.[4] Clinically, this lesion has been related to ectopic tubal pregnancy[4-6] and infertility.[1,5,7-11] Although the incidence is not known, Honore[5] reported an occurrence of 2.86% in a group of patients with tubal ectopic pregnancy and 50% in a group of infertility patients.

Salpingitis isthmica nodosa is often bilateral and usually characterized by a fusiform, nodular swelling in the isthmic section of the oviduct but rarely may affect the ampullary portion as well. The typical histologic features are chronic salpingitis and cystic diverticula of the mucosa within the muscle wall. Bundey and Williams[12] considered this lesion to be neoplastic, because no chronic inflammation was present and because a tumorlike swelling was found. Although there appear to be no other reports in the literature to support the neoplastic potential of SIN, this lesion has been described as progressive and capable of involving the whole oviduct.[11]

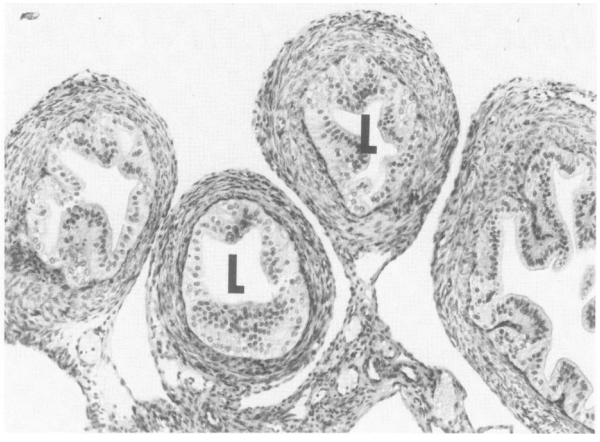
Animal Model

Changes similar to those described in women can be induced in mice by subcutaneously injecting outbred female CD-1 mice [Crl:CD-1 (ICR) BR] with diethylstilbestrol (DES) dissolved in corn oil on Days 1 to 5 of neonatal life (2 μg/pup/day). Controls receive corn oil alone (Figure 1).

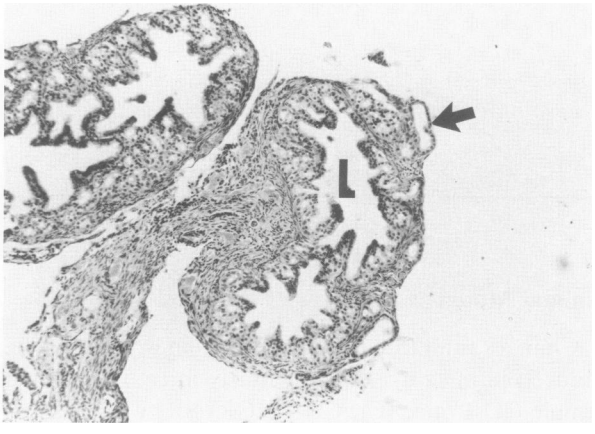
The hormonal treatment results in oviductal alterations in 100% of the exposed mice. At 1 month of age, focal epithelial hyperplasia is observed, with a single diverticulum extending into the muscle wall (Figure 2). Epithelial hyperplasia with epithelial folds extending through the muscularis is present by 2–4 months. Some of the folds split the muscle wall, which results in another layer of connective tissue around the epithelial elements. These glandlike structures connect with the oviductal lumen. The lesion progresses, and by 6 months of age there is marked epithelial proliferation with ex-

Publication sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and supported by Public Health Service Grant RR-00301 from the Division of Research Resources, National Institutes of Health, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

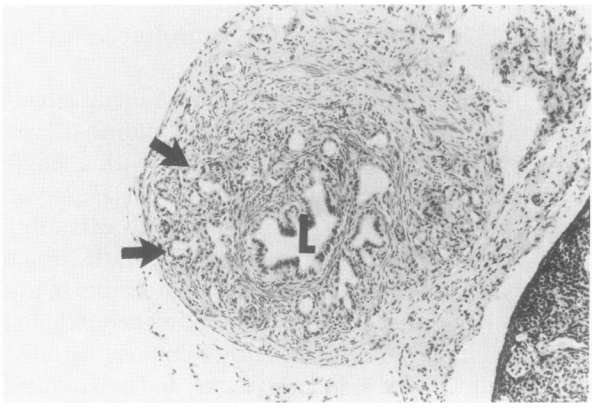
Address reprint requests to Dr. Retha R. Newbold, Laboratory of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709.



1



2



3

Figure 1 — Photomicrograph of the isthmic segment of the oviduct of an adult CD-1 control mouse. Tortuous coiling of the oviduct results in several cross sections in this illustration. *L*, oviductal lumen. (H & E, ×35) **Figure 2** — Photomicrograph of the isthmic segment of the oviduct of a 1-month-old mouse receiving DES on Days 1-5 of neonatal life. The epithelial folds are of normal height, but the epithelium extends into and through the muscularis (*arrow*), *L*, oviductal lumen. (H & E, ×30) **Figure 3** — Photomicrograph of a section of the isthmic portion of the oviduct from a 6-month-old mouse given DES on Days 1-5 of neonatal life. The lumen (*L*) is surrounded by a thickened wall containing glandlike spaces lined by tubal epithelium (*arrow*). (H & E, ×30)

tension into and through the muscularis (Figure 3). This results in an irregular serosal surface. There is no apparent connection of some glandular structures with the lumen, and the entire circumference of the oviduct may be affected. Although epithelial proliferation is extensive, this lesion does not spread along the serosal surface to other organs, and metastases are not observed. Similar morphologic lesions are not observed in the oviducts of untreated control mice at corresponding ages and at various stages of the estrus cycle.

Comparison With Human Disease

SIN in mice and SIN in humans show many similarities. In both species, diverticuli of the oviductal mucosa extend into the muscle wall, forming pseudoglandular islets of epithelium surrounded and enclosed by connective tissue. In addition, the lesion is progressive and may or may not be associated with secondary inflammation. SIN can be localized in any segment of the oviduct in both species. Although connective tissue hyperplasia of the isthmic segment of the oviduct in humans is a common histologic characteristic, this feature is not generally present in mice. These stromal changes observed in women may be due to secondary inflammation. In both species, SIN is associated with infertility, and in women it is related to ectopic pregnancy.

Prenatal exposure to DES has been linked to a variety of teratogenic and carcinogenic effects in the female offspring of humans. Alterations in müllerian-duct-derived tissues appear to be a common denominator in the observed abnormalities. Animal studies have demonstrated similar lesions in the uterus, cervix, and vagina of mice exposed prenatally or neonatally to DES.[13-16] Reports of oviductal malformation in experimental[13,17] and clinical[18] studies as well as increased incidences of ectopic pregnancy[18] suggest that the oviduct is also one of the affected müllerian-duct-derived tissues. A recent study describes SIN, similar to the DES-exposed lesion in mice, in the oviduct of a woman exposed prenatally to DES.[19]

Usefulness of the Model

The induction of SIN in mice provides a useful model for the study of the pathogenesis of hormonally induced lesions of the oviduct and possibly other developmental malformations. This animal model will permit the study of control mechanisms that can be used in treatment. It further should be useful in determining the relationship of diverticulosis and inflammation in the pathogenesis of SIN.

References

1. Benjamin CL, Beaver DC: The pathogenesis of salpingitis isthmica nodosa. Am J Clin Pathol 1951, 21:212–222
2. Benirschke K: The Mammalian Oviduct. Chicago, The University of Chicago Press, 1969, pp 271–307
3. Burne JC: Salpingitis isthmica nodosa, Postgraduate Obstetrical and Gynecological Pathology. Edited by H Fox, FA Langely. New York, Pergamon Press, 1973, pp 259–279
4. Freakley G, Normal WJ, Ennis JT, et al: Diverticulosis of the fallopian tubes. Clin Radiol 1974, 25:535–542
5. Honore LH: Salpingitis isthmica nodosa in female infertility and ectopic tubal pregnancy. Fertil Steril 1978, 29:164–168
6. Majmudar B, Henderson PH III, Semple E: Salpingitis isthmica nodosa: A high risk factor for tubal pregnancy. Obstet Gynecol 1983, 62:73–78
7. Craig JM: The pathology of infertility. Pathol Annu 1975, 10:299–328
8. deBrux J, Palmer R, Monteforte C: Étude histologique et pronostic des lésions tubaries dans la sterilité. Gynecol Obstet (Paris) 1969, 68:11–24
9. Thomas ML, Rose DH: Salpingitis isthmica nodosa demonstrated by hysterosalpingography. Acta Radiol 1973, 14:295–304
10. Woodruff JD, Pauerstein CJ: The Fallopian Tube. Baltimore, Williams Wilkins, 1969, pp 117–150
11. Cioltei A, Tasca L, Titiriga L, Maakaron G, Calciu V: Nodular salpingitis and tubal endometriosis: II. Diagnosis and differential diagnosis. Acta Eur Fertil 1979, 10:147–160
12. Bundey JG, Williams JD: Salpingitis isthmica nodosa with tumour formation resembling torsion of an ovarian cyst. J Obstet Gynaec Br Commonw 1963, 70:519–522
13. McLachlan JA, Newbold RR, Bullock BC: Long term effects on the female mouse genital tract associated with prenatal exposure to diethylstilbestrol. Cancer Res 1980, 40:3988–3999
14. Bern H, Talamantes FJ: Developmental Effects of Diethylstilbestrol (DES) in Pregnancy. Edited by AL Herbst, H Bern. New York, Thieme-Stratton, 1981, p 129–147
15. Newbold RR, Tyrey S, Haney AF, McLachlan JA: Developmentally arrested oviduct: A structural and functional defect in mice following prenatal exposure to diethylstilbestrol. Teratology 1983, 27:417–426
16. Newbold RR, Bullock BC, McLachlan JA: Exposure to diethylstilbestrol during pregnancy permanently alters the ovary and oviduct. Biol Rep 1983, 28:735–744
17. Newbold RR, McLachlan JA: Vaginal adenosis and adenocarcinoma in mice exposed prenatally or neonatally to diethylstilbestrol. Cancer Res 1982, 42:2003–2011
18. DeCherney AH, Cholst I, Naftolin F: Structure and function of the fallopian tubes following exposure to diethylstilbestrol (DES) during gestation. Fertil Steril 1981, 36:741–745
19. Shen SC, Bansal M, Purrazzella R, Malviya V, Strauss L: Benign glandular inclusions in lymph nodes, endosalpingiosis and salpingitis isthmica nodosa in a young girl with clear cell adenocarcinoma of the cervix. Am J Surg Pathol 1983, 7:293–300