Endometriosis is an entity with extreme pleiomorphism

G.Leyendecker

Department of Obstetrics and Gynaecology, Klinikum Darmstadt, Academic Teaching Hospital to the University of Frankfurt, Darmstadt, Germany

This debate was previously published on Webtrack 90, October 13, 1999

Endometriosis and adenomyosis have long been considered as one entity with a common, although unknown, aetiology (Meyer, 1919). After the term endometriosis was coined (Sampson, 1927), it was widely used for the intrauterine and the extrauterine variety of the disease respectively (Counseller, 1938). However, it was the theory of tubal spread of normal endometrial cells by retrograde menstruation as the cause of pelvic endometriosis (Sampson, 1927) that finally led to consideration of both localizations of ectopic endometrial growth as different entities. If Sampson's theory were correct, then infiltrative and expansive growth of endometrial glands and stroma with hyperplasia of surrounding muscular tissue into the depth of the myometrium would differ from pelvic endometriosis not only by localization but also by pathogenesis. Consequently, although the frequent association of endometriosis with adenomyosis was recognized (Emge, 1962; Pratt, 1972), it was suggested that the term 'endometriosis' should be used exclusively for endometrial growth beyond the confines of the uterus and that the term 'adenomyosis' should be used only for intrauterine ectopic endometrial growth (Ridley, 1968).

Recently, it was suggested that there were three types of endometriotic lesions, peritoneal, ovarian and rectovaginal (Nisolle and Donnez, 1997). While peritoneal endometriosis would result from transtubal shedding and implantation of endometrial cells, ovarian endometriomata would result from metaplasia and rectovaginal endometriosis, with endometrial glands and stroma as well as muscular tissue displaying the composition of adenomyomata, would arise from Müllerian remnants.

It has been suggested the existence of principally two phenotypes of endometriosis, superficial endometriosis including ovarian endometriomata and adenomyosis (Brosens, 2000). While superficial endometriosis would arise from the shedding of superficial endometrium (SE) (and the term endometriosis should be restricted to this variety), adenomyosis would result from basal endometrium (BE) and the subendometrial myometrium (junctional zone myometrium; JZM; archimyometrium) (Werth and Grusdew, 1898; Noe *et al*., 1999) and would preferentially present at certain locations (Cullen, 1920), particularly the uterine myometrium, the uterine ligaments and the rectovaginal septum. Superficial endometriosis would not develop into deep infiltrative endometriosis, because they both were different entities.

We have recently suggested that endometriosis originates at the uterine level and constitutes primarily a disease of the archimetra (Leyendecker *et al*., 1998; Noe *et al*., 1999) since altered endometrial cells with a higher potential for growth on peritoneal surfaces gain access to the peritoneal cavity, and so adenomyosis merely constitutes a special variant of endometriosis. Meanwhile, we have extended our studies and found further evidence that pelvic endometriosis with all its phenotypes are sequelae of uterine adenomyosis or its early manifestations, and that both endometriosis and adenomyosis constitute a pathogenetic entity (Kunz *et al.*, 2000). Several lines of evidence support this notion.

Firstly, the eutopic endometrium in endometriosis shows alterations similar to those which occur in the endometriotic lesions that are not found in the endometrium of women free of disease. These alterations include signs of increased inflammatory response, such as the increased expression of monocyte-chemotactic protein-1 (MCP-1) (Jolicoeur *et al*., 1998) and the increased colonization with macrophages (Leiva *et al*., 1994), signs of increased proliferation (Wingfield *et al*., 1995) and of increased biochemical activity, e.g. pathological expression of *P*450 aromatase (Noble *et al*., 1996; 1997) resulting in increased tissue concentrations of oestradiol (Takahashi *et al*., 1989).

Secondly, women with endometriosis show a significant increase in uterine peristaltic activity in comparison to women free of disease. At mid-cycle, in women with endometriosis, the peristaltic activity becomes dysperistaltic, resulting in a breakdown of directed sperm transport (Leyendecker *et al*., 1996). Moreover, in women with endometriosis the intrauterine pressure is increased in comparison with women without the disease (Bulletti *et al*., 1997; Mäkäräinen, 1988).

Finally, in endovaginal sonography (EVS) and magnetic resonance imaging (MRI), women with endometriosis exhibit a significant expansion of the archimyometrium ('halo' in EVS or 'junctional zone' in MRI respectively) over controls, which is similar or identical to the images obtained in adenomyosis (Leyendecker *et al*., 1998; Kunz *et al*., 2000). The depth of the archimetrial invasion was correlated with the age of the patients. Histologically, this expansion involves all components of the archimetra such as the glandular and stromal endometrium as well as the subendometrial myometrium (M.Herbertz, M.Noe, G.Kunz, G.Mall and G.Leyendecker, unpublished data).

With respect to both, uterine hyper- and dysperistalsis as well as archimetrial expansion in women with endometriosis there was no correlation between the extent of these alterations and the grade of the disease (Leyendecker *et al*., 1996; Kunz *et al*., 2000). Thus, there was no indication that in minimal and mild endometriosis (superficial endometriosis) the archimetra (BE/JZM; Brosens, 2000) was not involved in the disease process. In contrast, the data indicate that there are uterine dysfunctions and adenomyotic changes of the archimetra or its early manifestations in all phenotypes of endometriosis, e.g. superficial or infiltrative endometriosis.

If our theory is correct that adenomyosis and its early manifestations constitute the primary lesion with pelvic endometriosis being merely a sequel, then the aetiology of endometriosis is primarily the aetiology of adenomyosis.

As the prevalence of adenomyosis is very high (Bird *et al*., 1972) its cause or causes are most probably not spectacular but rather related to the normal process of reproduction.

Trauma such as induced by pregnancy and delivery followed by endometrial proliferation into muscular dehiscencies has been long discussed (Emge, 1962; Ferenczy, 1998) and gained recent support by circumstantial evidence derived from the finding of adenomyosis following endometrial ablation (McLucas, 1994; Yuen, 1995; McCausland and McCausland, 1996). Adenomyosis has been characterized as the disease of the parous pre- and peri-menopausal woman (Parazzini *et al*., 1996) with the highest incidence during the fourth and fifth decade of life (Bird *et al*., 1972). Our own data have shown that adenomyosis is also present in young infertile women with endometriosis (Kunz *et al*., 2000) and in particular in those with severe dysmenorrhoea (G.Leyendecker, unpublished).

We have recently suggested that it is the specific morphological structure of the archimetra and its specific function of directed sperm transport that predisposes to chronic microtraumatization and chronic inflammatory and proliferatory response at the fundo-cornual raphe of the archimyometrium in the midline of the anterior and posterior wall of the uterus that results from the fusion of the two paramesonephric ducts (Werth and Grusdew, 1898; Leyendecker *et al*., 1998; Noe *et al*., 1999). There, the circular fibres of the stratum subvasculare form, in fundal direction, a decreasing angle as they separate into those of the cornua and the tubes (Figure 1). With respect to directed sperm transport, the unpaired uterus is still functioning as a paired organ (Kunz *et al*., 1998a) which, in view of its continuous action must lead, in time, to muscular distensions at the fundo–cornual raphe. Within 1 min following application of technitium-labelled macrospheres of sperm size at the cervical os, ~30% of the radioactivity reaches the tubes, thus demonstrating the enormous power of the uterine peristaltic pump (Figure 5 in Kunz *et al*., 1996). Sonographically, discontinuations of the 'halo' of the archimyometrium that represent endometrial infiltrations usually first appear in the midline of the uterine corpus (G.Leyendecker, unpublished data) (Figure 2) as does focal thickening of the 'junctional zone' in MRI (Figure 15 in Reinhold *et al*., 1998).

According to recent data (Prefontaine *et al*., 1990; Noble *et al*., 1996; Kitawaki *et al*., 1997), the *P*450 aromatase is not expressed in normal endometrium. However, our own data indicate that, in normal endometrium and the underlying myometrium, a transient expression of this enzyme occurs in the very early proliferative phase of the menstrual cycle (J.Becker, M.Noe, G.Kunz, G.Leyendecker, C.Noe, unpublished data). In adenomyotic tissue, in the eutopic endometrium of women with endometriosis as well as in endometriotic tissue such as the stroma of an ovarian endometrioma high expression of *P*450 aromatase could be demonstrated (Yamamoto *et al*., 1993; Noble *et al*., 1996, 1997; Kitawaki *et al*., 1997). The expression of *P*450 aromatase in adenomyotic/endometriotic tissue may, therefore, be viewed as pathological in that it appears to be continuously expressed in comparison to normal endometrium. It is, however unclear, whether the expression of *P*450 aromatase is resulting from chronic proliferative processes at the level of the basal endometrium or whether the chronic expression of this enzyme constitutes one of the initial events. In any event, the chronic expression of *P*450 aromatase results in chronically increased tissue

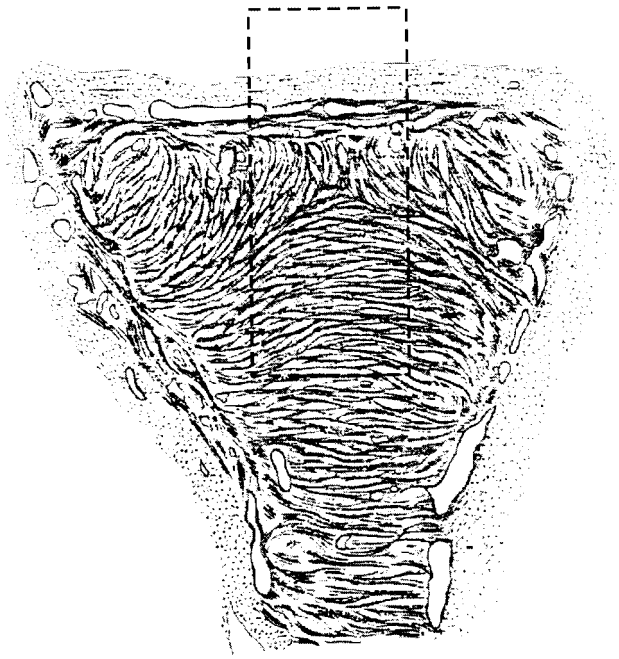

Figure 1. Modified original drawing from Werth and Grusdew (1898) showing the architecture of the subendometrial myometrium (archimyometrium) in a human fetal uterus. The specific orientation of the circular fibres of the archimyometrium results from the fusion of the two paramesonephric ducts forming a fundo–cornual raphe (Noe *et al*., 1999) in the midline (dashed rectangle). The peristaltic pump of the uterus, which is continuously active during the menstrual cycle, is driven by co-ordinated contractions of these muscular fibres. Directed sperm transport into the dominant tube is made possible by differential activation of these fibres. By the time muscular distensions at the fundo–cornual raphe result in the formation of gaps and the endometrial stroma loses, at the endometrial–myometrial interface, its functional counterpart that results in endometrial proliferation into these gaps. This figure is reproduced from *Arch. Gynäkol*., Untersuchungen über die Entwicklung und Morphologie der menschlichen Uterusmuskulatur. Werth and Grusdew, **55**, 325–409, Figure 6, 1898,

concentrations of oestrogen with various feed-forward effects as delineated recently (Leyendecker *et al*., 1998). Hyper- and dysperistalsis (Leyendecker *et al*., 1996) as well as increased intrauterine pressure (Mäkäräinen, 1988; Bulletti *et al*., 1997) may result from locally-increased oestrogen concentrations (Kunz *et al*., 1998b) as well as from archimetrial hyperproliferation that may both in turn increase chronic trauma.

Cells with an increased but varying potential of proliferation (Gaetje *et al*., 1995; Wingfield *et al*., 1995; Starzinski-Powitz *et al*., 1998) gain access to the peritoneal cavity where they implant and develop into endometriosis. In addition to the invasive potential of the cells, local factors may determine whether or not infiltrative endometriosis ensues (Koninckx *et al*., 1998). Infiltrative growth is usually restricted to the urinary bladder, the rectum, the sacrouterine ligaments and the recto-vaginal septum.

The seeding of altered cells by adenomyosis may change during the course of the disease. Profuse seeding in the beginning may decrease with adenomyotic nodule growth into the depth of the myometrium, leaving the superficial

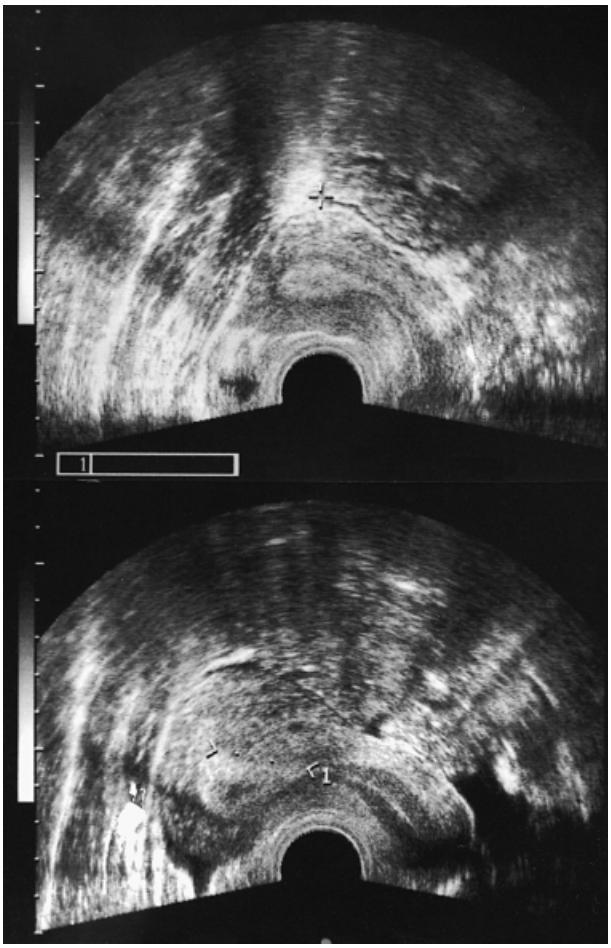

Figure 2. Endovaginal sonography of the anteflected uterus of a 33 year old woman without dysmenorrhoea and without endometriosis. In the sagital image of the whole uterus the archimyomterium ('halo') encircling the endocervix and the endometrium is completely intact (above). Endovaginal sonography of the anteflected uterus of a 33 year old woman with dysmenorrhoea and endometriosis. Endometriotic scars and adhesions were present on the peritoneum of the urinary bladder, the left ovarian fossa and the left sacro–uterine ligament. There were no ovarian endometriomata and both tubes were patent. In the sagital image the archimyometrium is intact in the cervical region and the anterior wall of the uterine corpus. In the posterior wall the normal 'halo' is destroyed (calipers) by pathological archimetrial infiltration into the depth of the myometrium. Together with the thickening of the posterior uterine wall this is indicative of diffuse adenomyosis and explains both, dysmenorrhoea and infertility that had been considered as idiopathic (below).

endometrium intact. This may be the reason why there was less expression of *P*450 aromatase (Noble *et al*., 1996) and no deficiency in 17βHSD type 2 (Zeitoun *et al*., 1998) in the eutopic endometrium of women with endometriosis obtained by curettage in comparison to endometriotic lesions. Seeding might even come to a halt when the adenomyotic nodule might have 'burnt out'. This might be the basis for the finding of only endometriotic scars during laparotomy and of the notion that every woman has endometriosis once in her life (Evers, 1994).

The natural history of adenomyosis as delineated above may explain the extreme variability or pleiomorphism of the clinical appearance of endometriosis. The latter may be completely asymptomatic and may be found at a prevalence of up to 30% during laparoscopic sterilization in women with their last pregnancy 10 or more years ago (Moen, 1991). Archimetrial invasion into the depth of the myometrium may explain persisting subfertility and dysmenorrhoea in women with minimal-to-mild endometriosis following eradication of the endometriotic lesions (Hull *et al*., 1986; Adamson and Pasta, 1994; Leyendecker *et al*., 1996; Wood, 1998). Little invasion into the myometrium may explain the absence of discomfort and dysmenorrhoea in some patients that present with diffuse peritoneal endometriosis including ovarian endometriomata (G.Leyendecker, unpublished). Infiltrative endometriosis such as recto–vaginal endometriosis might persist in the presence of ceased seeding from the uterine adenomyotic nodule, while the superficial endometriotic lesions might have healed resulting in the impression of recto–vaginal endometriosis as a singular entity. Finally, adenomyosis might penetrate the uterine serosa with ensuing massive peritoneal endometriosis (Jones and Jones, 1981).

As pelvic endometriosis, with all its phenotypes, primarily results, in our opinion, from adenomyotic lesions that constitute a pathological proliferation of all components of the archimetra this part of the uterus with its endo-, para- and autocrine regulation as well as with its cell–cell interaction at the endometrial–archimyometrial interface (Fujii *et al*., 1989; Brosens *et al*., 1998) should become a focus of research. The unravelling of these mechanisms might contribute to the understanding, how chronic trauma might induce chronic proliferative and invasive processes and why, on what level and to what extent hereditary mechanisms (Kennedy, 1997) and environmental factors such as endocrine disrupters (Rier *et al*., 1993; Bois and Eskenazi, 1994; Koninckx *et al*., 1994; Eskenazi and Kimmel, 1995; Mayani *et al*., 1997; Tsai *et al*., 1997; Kuchenhoff *et al*., 1999) become operative in this respect and why, finally, some women develop the disease early in their lives.

In conclusion, the uterus as a phylogenetically paired organ has become unpaired in the human, by the fusion of the two paramesonpehric ducts during early ontogeny. With respect to rapid and sustained directed sperm transport, however, the uterus has maintained the function of a paired organ. The function of directed sperm transport is made possible by the specific architecture of the archimyometrium that is characterized by a fundo-cornual raphe (Werth and Grusdew, 1898; Noe *et al*., 1999). Both morphology and function predispose to chronic microtrauma with muscular distensions and reactive proliferation and invasion of the endometrium into the myometrium with metaplastic changes of the stroma into archimetrial myometrium resulting in adenomyosis. The adenomyotic foci may seed altered cells with an increased but variable potential of implantation and infiltrative growth into the peritoneal cavity with the tubes being the usual but not the exclusive route. The natural history of adenomyosis as the underlying disease, the quality of the spread cells as the seed as well as the topography and the response of the peritoneal cavity with its serosa and its organs as the bed determine the pleiomorphism of endometriosis.

References

Adamson, G.D. and Pasta, D.J. (1994) Surgical treatment of endometriosis-associated infertility: analysis compared with survival analysis. *Am. J. Obstet. Gynecol.*, **171**, 1488–1505.

Bird, C.C., McElin, T.W. and Manalo-Estrella, P. (1972) The elusive adenomyosis of the uterus-revisited. *Am. J. Obstet. Gynecol.*, **112**, 583–593.

Bois, F.Y. and Eskanazi, B. (1994) Possible risk of endometriosis for Seveso, Italy, residents: an assessment of exposure to oxytocin. *Environ. Health Perspect.*, **102**, 476–477.

Brosens, I.A. (2000) Redefining endometriosis: is deep endometriosis a progressive disease? *Hum. Reprod.*, **15**, in press.

Brosens, J.J., Barker, F.G. and de Souza, N.M. (1998) Myometrial zonal differentiation and uterine junctional zone hyperplasia in the non pregnant uterus. *Hum. Reprod. Update*, **4**, 496–502.

Bulletti, C., Rossi, S., de Ziegler, D. *et al.* (1997) The uterine contractility in endometriosis. [Abstr.] In *International Meeting on Infertility and Assisted Reproductive Technology*, *Porto Cervo*, *Italy*, *June 11–14*, ***1997***, *Abstract Book*, p. 129.

Counseller, V.S. (1938) Endometriosis. *Am. J. Obstet. Gynecol.*, **36**, 877–888.

Cullen, T.S. (1920) The distribution of adenomyoma containing uterine mucosa. *Arch. Surg.*, **1**, 215–283.

Emge, L.A. (1962) The elusive adenomyosis of the uterus. *Am. J. Obstet. Gynecol.*, **83**, 1541–1563.

Eskenazi, B. and Kimmel, G. (1995) Workshop on perinatal exposure to dioxin-like compounds. II. Reproductive effects. *Environ. Health Perspect.*, **103** (Suppl. 2), 143–145.

Evers, J.L.H. (1994) Endometriosis does not exist; all women have endometriosis. *Hum. Reprod.*, **9**, 2206–2209.

Ferenczy, A. (1998) Pathophysiology of adenomyosis. *Hum. Reprod. Update*, **4**, 312–322.

Fujii, S., Konishi, I. and Mori, T. (1989) Smooth muscle differentiation at endometrio–myometrial junction. An ultrastructural study. *Virch. Archiv A Pathol. Anat.*, **414**, 105–112.

Gaetje, R., Kotzian, S., Herrmann, G. *et al.* (1995) Invasiveness of endometriotic cells *in vitro. Lancet*, **346**, 1463–1464.

Hull, M.E., Moghissi, K.S., Magyar, D.F. and Hayes, M.F. (1986) Comparison of different treatment modalities of endometriosis in infertile women. *Fertil. Steril.*, **47**, 40.

Jolicoeur, C., Boutouil, M., Drouin, R. *et al.* (1998) Increased expression of monocyte chemotactic protein-1 in the endometrium of women with endometriosis. *Am. J. Pathol.*, **152**, 125–133.

Jones, H.W. and Seegar Jones, G. (1981) *Novak's Textbook of Gynecology.* 10th edn. Williams and Wilkins, Baltimore and London, pp. 443.

Kennedy, S. (1997) Is there a genetic basis to endometriosis? *Semin. Reprod. Endocrinol.*, **15**, 309–318.

Kitawaki, J., Noguchi, T., Amatsu, T. *et al.* (1997) Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. *Biol. Reprod.*, **57**, 514–519.

Koninckx, P.R., Kennedy, S.H. and Barlow, D.H. (1998) Endometriotic disease: the role of peritoneal fluid. *Hum. Reprod. Update*, **4**, 741–751.

Koninckx, P.R., Braet, P., Kennedy, S.H. and Barlow, D.H. (1994) Dioxin pollution and endometriosis in Belgium. *Hum. Reprod.*, **9**, 1001–1002.

Kuchenhoff, A., Seliger, G., Klonisch, T. *et al.* (1999) Arylhydrocarbon receptor expression in the human endometrium. *Fertil. Steril.*, **71**, 354–360.

Kunz, G., Beil, D., Deininger, H. *et al.* (1996) The dynamics of rapid sperm transport through the female genital tract. Evidence from vaginal sonography of uterine peristalsis (VSUP) and hysterosalpingoscintigraphy (HSSG). *Hum. Reprod.*, **11**, 627–632.

Kunz, G., Herbertz, M., Noe, M. and Leyendecker, G. (1998a) Sonographic evidence of a direct impact of the ovarian dominant structure on uterine function during the menstrual cycle. *Hum. Reprod. Update*, **4**, 667–672.

Kunz, G., Noe, M., Herbertz, M. and Leyendecker, G. (1998b) Uterine peristalsis during the follicular phase of the menstrual cycle. Effects of oestrogen, antioestrogen and oxytocin. *Hum. Reprod. Update*, **4**, 647–654.

Kunz, G., Beil, D., Huppert, P. and Leyendecker, G. (2000) Structural abnormalities of the uterine wall in women with endometriosis and infertility visualised by vaginal sonography and magnetic resonance imaging. *Hum. Reprod.*, **15**, in press.

Leiva, M.C., Hasty, L.A. and Lyttle, C.R. (1994) Inflammatory changes of the endometrium in patients with minimal-to-moderate endometriosis. *Fertil. Steril.*, **62**, 967–972.

Leyendecker, G., Kunz, G., Wildt, L. *et al.* (1996) Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. *Hum. Reprod.*, **11**, 1542–1551.

Leyendecker, G., Kunz, G., Noe, M. *et al.* (1998) Endometriosis: a dysfunction and disease of the archimetra. *Hum. Reprod. Update*, **4**, 752–762.

Mäkäräinen, L. (1988) Uterine contractions in endometriosis: effects of operative and danazol treatment. *J. Obstet. Gynecol.*, **9**, 134–138.

McCausland, A.M. and McCausland, V.M. (1996) Depth of endometrial penetration in adenomyosis helps determine outcome of rollerball ablation. *Am. J. Obstet. Gynecol.*, **174**, 1786–1794.

McLucas, B. (1994) Does endometrial resection cause adenomyosis? *J. Am. Assoc. Gynecol. Laparosc.*, **1** (4, Part 2), S21.

Meyer, R. (1919) Über den Stand der Frage der Adenomyositis und Adenome im allgemeinen und insbesondere über Adenomyositis seoepithelialis und Adenomyometritis sarcomatosa. *Zbl. Gynäk.*, **43**, 745–750.

Mayani, A., Barel, S., Soback, S. and Almagor, M. (1997) Dioxin concentrations in women with endometriosis. *Hum. Reprod.*, **12**, 373–375.

Moen, M.H. (1991) Is a long period without childbirth a risk factor for developing endometriosis? *Hum. Reprod.*, **6**, 1404.

Nisolle, M. and Donnez, M. (1997) Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil. Steril.*, **68**, 585–596.

Noble, L.S., Simpson, E.R., Johns, A. and Bulun, S.E. (1996) Aromatas expression in endometriosis. *J. Clin. Endocrinol. Metab.*, **81**, 174–179.

Noble, L.S., Takayama, K., Zeitoun, K.M. *et al.* (1997) Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. *J. Clin. Endocrinol. Metab.*, **82**, 600–606.

Noe, M., Kunz, G., Herbertz, M. *et al.* (1999) The cyclic pattern of the immunocytochemical expression of oestrogen and progesterone receptors in human myometrial and endometrial layers: characterization of the endometrial–subendometrial unit. *Hum. Reprod.*, **14**, 190–197.

Parazzini, F., Vercellini, P., Panazza, S. *et al.* (1997) Risk factors for adenomyosis. *Hum. Reprod.*, **12**, 1275–1279.

Pratt, J.H. (1972) The elusive adenomyosis of the uterus – revisited. Discussion. *Am. J. Obstet. Gynecol.*, **112**, 591–592.

Prefontaine, M. Shih, C., Pan, C.C. and Bhavnani, B.R. (1990) Applicability of the product isolation and the radiometric aromatase assays for the measurement of low levels of aromatase: lack of aromatse activity in the human endometrium. *J. Endocrinol.*, **127**, 539–551.

Reinhold, C., Tafazoli, F. and Wang, L. (1998) Imaging features of adenomyosis. *Hum. Reprod. Update*, **4**, 337–349.

Ridley, J.H. (1968) The histogenesis of endometriosis. *Obstet. Gynecol. Surv.*, **23**, 1–35.

Rier, S.E., Martin, D.C., Bowman, R.E. *et al.* (1993) Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Fundam. Appl. Toxicol.*, **21**, 433–441.

Sampson, J.A. (1927) Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am. J. Obstet. Gynaecol.*, **14**, 422–429.

Starzinski-Powitz, A., Gaetje, R., Kotzian, S. *et al.* (1998) Tracing cellular and molecular mechanisms involved in endometriosis. *Hum. Reprod. Update*, **4**, 724–729.

Takahashi, K., Nagata, H. and Kitao, M. (1989) Clinical usefulness of determination of estradiol levels in the menstrual blood for patients with endometriosis. *Acta Obstet. Gynecol. Jpn*, **41**, 1849–1850.

Tsai, M.L., Webb, R.C. and Loch-Caruso, R. (1997) Increase in oxytocin-induced oscillatory contractions by 4-hydrated-2′,4′, 6'-trichlorobiphenyl is estrogen receptor mediated. *Biol. Reprod.*, **56**, 341–347.

Werth, R. and Grusdew, W. (1898) Untersuchungen über die Entwicklung und Morphologie der menschlichen Uterusmuskulatur. *Arch. Gynäkol.*, **55**, 325–409.

Wingfield, M., Macpherson, A., Healy, D.L. and Rogers, P.A.W. (1995) Cell proliferation is increased in the endometrium of women with endometriosis. *Fertil. Steril.*, **64**, 340–346.

Wood, C. (1998) Surgical and medical treatment of adenomoysis. *Hum. Reprod. Update*, **4**, 323–336.

Yamamoto, T., Noguchi, T., Tamura, T. *et al.* (1993) Evidence for oestrogen synthesis in adenomyotic tissues. *Am. J. Obstet. Gynecol.*, **169**, 734–738.

Yue, P.M. (1995) Adenomyosis following endometrial rollerball ablation. *Aust. N.Z. J. Obstet. Gynaecol.*, **35**, 335–336.

Zeitoun, K., Takayama, K., Sasano, H. *et al.* (1998) Deficient 17β-hydroxysteroid dehydrogenase type 2 expression in endometriosis: failure to metabolize 17β-estradiol. *J. Clin. Endocrinol. Metab.*, **83**, 4474–4480.