SCIENCE & PRACTICE

Pathogenesis of endometriosis

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Endometriosis may be defined as the presence of functioning endometrial glands and stroma outside their usual location lining the uterine cavity. It has been identified in virtually all tissues and organs of the female body with the exception of the spleen, which seems to enjoy immunity to this disease process.

Causation

The development of endometriosis, no matter where the location, is probably a multifactorial event. Many theories relating to the aetiology of endometriosis have been proposed. These hypotheses have been divided into four groups: transport, coelomic metaplasia, embryonic cell rests, and numerous immunological theories. The most widely accepted transportation theory suggests that viable endometrial cells reflux through the fallopian tubes during menstruation and implant and grow on the surrounding pelvic structures and peritoneum. This theory is lent support by data showing an increased occurrence of endometriosis in women with Mullerian duct anomalies resulting in an obstructed genital outflow tract and thus increased retrograde menstruation. Added to this are epidemiological data suggesting that women who menstruate more frequently, more heavily, or for a longer duration of time, and therefore have increased exposure to retrograde menstruation, also have a higher risk of developing the disease.

These data suggest that any exposure of the pelvic and abdominal peritoneum to menstrual reflux would result in an increased risk of endometriosis. Unfortunately, this single cause and effect relation is weakened by several factors, such as the observation that 90% of women with patent fallopian tubes have bloody peritoneal fluid if they are laparoscoped during the perimenstrual period,[1] yet the prevalence of endometriosis in reproductive age women is reported by one investigator to be only 2–5%.[2] Other transport theories include dissemination of endometrial fragments through lymphatics and blood vessels and inadvertent iatrogenic dissemination during abdominal or pelvic surgery. Lymphatic and haematogenous dissemination does provide an attractive explanation for the occurrence of endometriosis at locations outside the abdominal cavity. Vascular metastasis of endometrial fragments has been observed; and a necropsy study evaluating a group of patients with pelvic endometriosis showed that 29% had pelvic lymph-nodes containing endometrial-like glands or stroma, or both.[3]

The coelomic metaplasia hypothesis states that peritoneal mesothelium undergoes metaplasia, forming typical endometrial-like glands and stroma. This theory would explain endometriosis in women with Mullerian agenesis, who have an absent uterus or a hypoplastic non-functioning uterus, or the occasional presence of endometriosis in men. The embryonic cell rests theory is that the developing Mullerian duct system may leave behind small clusters or rests of Mullerian cells that have the potential to develop into functioning endometrial-like tissue. Since no cell rests of this type have been documented, however, this proposal remains only speculative.

The possibility that the development and progression of endometriosis is associated with abnormal immune function is the most recent hypothesis for the aetiology of this disease process. Over the past 10–15 years, various data have suggested alterations in both cell-mediated and hormonal immunity in women with endometriosis. Whether this immunological factor is a separate cause or a synergistic factor to one or more of the other causes is yet to be established. There is, however, little doubt that the immunological process does play a part in the development and progression of endometriosis.

Evidence for this relation comes from investigations in both animals and man. In two unrelated studies in which the immune system was suppressed in rhesus monkeys, by proton radiation[4] and by polychlorinated biphenyls,[5] endometriosis developed more frequently than in controls. Numerous workers have also identified changes in one or more factors of the immune system in women with this disease process. An early study by Weed and Arguembourg[6] identified the presence of C3 component of complement and IgG deposits in uterine endometrium of women with endometriosis, suggesting that in some way ectopic endometrium was related to an alteration of the immune process which was manifested by an immune reaction to normal endometrium. At roughly the same time, Mathur et al[7] identified IgG and IgA autoantibodies against ovarian and endometrial tissue in serum and in vaginal and cervical secretions of women with endometriosis. Unfortunately, some of these studies were not confirmed by other groups. Switchenko et al[8] were unable to show an association between increased anti-endometrial antibodies and endometriosis.

Halme[9] and Zeller[10] and their colleagues identified large numbers of activated macrophages in women with endometriosis, indicating that the endometriotic process was directly related to an immunological peritoneal reaction. It is noteworthy that these peritoneal macrophages from such women produce substantially more fibronectin, a growth factor for fibroblasts, than do macrophages from healthy women.[11]

Other evidence of peritoneal fluid from altered immunity includes work showing decreased cytotoxicity to endometrial cells attributable to a defect in natural killer cells.[12] This response may in part be due to an increased resistance to lysis by the endometrial cells.

These data taken together suggest that women with endometriosis have endometrial cells that are somewhat less sensitive to the normal body defence mechanisms and, as a result, implant and grow more easily in ectopic sites.

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contemplated. However, use of antisense oligonucleotides for ex-vivo marrow purging before autologous bone marrow transplantation would not run into such difficulties and might be a good approach to begin with.[6] Two such trials are likely to be started soon, one in Houston, Texas, and the other in London.

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Chariots of fear: wheelchair-related accidents

From time to time we are reminded of the dangers lurking in everyday objects. Thus Dudley and co-workers[1] draw attention to the frequency of accidents among wheelchair users and their carers. 48 of 174 users who completed a questionnaire reported the occurrence of accidents since receiving the chair—21 to the occupant, 16 to the attendant, and 11 to both. Of the 43 users who were interviewed and who had themselves been injured, almost all had sustained simple or multiple falls from the chair and 5 of them had had fractures. The 27 attendants involved in accidents had generally sustained mild injuries—for example, trauma to the shin, entrapment of fingers while erecting or dismantling the chair, and bruising. In a few cases the injuries were severe enough to necessitate hospital attendance. The researchers conclude that the annual number of such accidents in the UK alone would be well over 20 000. An earlier report from the same department[2] described the ramshackle condition of many hospital wheelchairs, and implicated faults in 5 of 11 accidents befalling their occupants. The commonest defects were malfunctioning brakes, soft or punctured tyres, absent or defective footrest plates, and torn arm-rest coverings, all of which are readily remedied. Hospital staff were also poorly informed about problems associated with wheelchairs.

In 1990, a US study[3] identified, from death certificates filed with the National Injury Information Clearinghouse, 770 wheelchair-related deaths between the years 1973 and 1987, although this figure was probably an underestimate due to under-reporting. Most of the casualties (66%) had fallen from the chair, which in other cases (11·4%) had itself tipped over. In 60·8% of cases the accident occurred in an institution or hospital, and in 27·5% at home. In 1987, it was estimated that there were 26 346 wheelchair-related accidents in the US serious enough for the victim to seek attention at an emergency room.[4]

Most wheelchairs are used by elderly people for short periods only and often less frequently than once a day. A report from a geriatric hospital in Toronto[5] recorded that almost half of all falls were related to a change of position or posture such as getting in and out of bed or a wheelchair, or on or off the toilet, and concluded that wheelchairs were a potential hazard to geriatric patients. At the other end of the scale are youthful, permanent occupants of their chairs—19 elite wheelchair athletes reported an astonishing 50 injuries over 1 year.[6] Although most incidents were sport related, 6 were not, including 3 athletes hurt during chair transfer who sustained two of the three fractures in this series. But hazards other than sport await the more adventurous wheelchair-bound spirit, and it is encouraging to learn that the design of restraints in vehicles transporting wheelchairs is now receiving attention in several countries.[7]

To put all these figures into perspective, there were about 400 000 wheelchair users in the UK a few years ago[8] and perhaps nearly 500 000 now. The number of users in the US is said to be 3·3/1000 persons,[3] or a total of over 800 000. Some dangers will inevitably accompany the enormously enhanced freedom of mobility conferred by a wheelchair. The toll of accidents is hardly immense, but there is a constant theme running through all these reports—that it could, by very simple means, be reduced further. Attention to environmental hazards such as kerbs and steps and unprotected stairs both in institutions and in private households is clearly important, and was emphasised in a recent wide-ranging survey of home accidents in older people, albeit without specific reference to wheelchairs.[9] The wider use of lapstraps, greater attention to maintenance of wheelchairs, and proper training of both user and carer in their use and in transferring in and out of them are measures that can help to eliminate the more avoidable of these misfortunes.

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Furthermore, the accompanying altered immune response acts inappropriately with the production of increased tissue growth factors such as fibronectin stimulating a fibrotic reaction that protects the endometriotic implants.

Prevalence

The prevalence of endometriosis in reproductive-aged women in world-wide publications is reported to be within the range 1–50%.[2] Jeffcoate[13] reported that endometriosis was found in 10–25% of women undergoing laparotomy by gynaecologists in the UK and the USA.[13]

Of 459 consecutive patients with primary infertility investigated at the Johns Hopkins Hospital, 114 (25%) proved to have endometriosis.[14] Verkauf[15] prospectively identified endometriosis in 38·5% of infertile women and 5·2% of fertile women. Other workers have confirmed that infertile women are 7–10 times more likely to have endometriosis than their fertile counterparts. Selection bias—ie, the selection of patients for which a particular type of operation was done—probably accounts for the wide variation in the reported prevalence.

Natural history

The natural history of endometriosis is not clearly understood. The disease seems to progress in most untreated women,[16] although spontaneous regression has been described in mild cases. Surgical and medical therapies might prevent a temporal progression. What is the effect of pregnancy on the clinical course of endometriosis? Although pregnancy is thought to induce involution of endometriotic implants, McArthur and Ulfelder[17] showed that the behaviour of endometriosis during the gravid state was highly variable, and regression of disease seemed to be due to decreased tissue responsiveness to hormonal stimulation rather than necrosis of lesions.

Symptoms

Dysmenorrhea, dyspareunia, and pelvic, back, and rectal pain are the more common symptoms described by women with endometriosis. These symptoms have been assumed to be caused by endometriotic implants; however, the development of such symptoms cannot be regarded as diagnostic of the disease state. The presence of laparoscopically diagnosed endometriosis in patients with chronic pelvic pain ranges from 4% to 52% in published series.[18]

Although deep infiltration of endometriosis into fibromuscular tissue of the pelvis has been strongly correlated with pelvic pain,[19] there is no universally accepted hypothesis that explains how endometriosis can cause the other common symptoms. Infertility is also commonly associated.

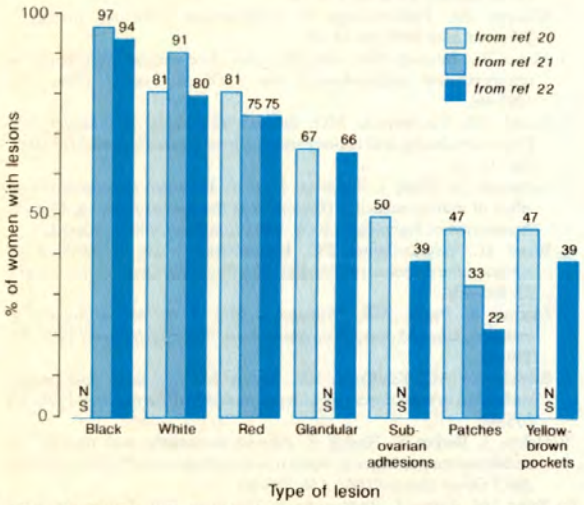

Fig 1—Percentage of various lesions, categorised by appearance, in women with histologically confirmed endometriosis.

Revised from ref 22, by permission of the author and Resurge Press. NS = not stated.

Diagnosis and classification

Endometriosis is suspected from the clinical history, and the diagnosis is confirmed by imaging techniques including ultrasonography, computed tomography, and magnetic resonance imaging. However, a true diagnosis can be made only by direct observation and biopsy showing typical glands or stroma or both. Although classic blue-black peritoneal implants of endometriosis are generally easily recognised, active disease hidden beneath fibrosis or non-classic disease consisting of white, red, or brown lesions requires histological confirmation (fig 1).

Donnez and co-workers[23] further elucidated the biological characteristics of peritoneal endometriosis. With an advanced stereographic computer technology for the investigation of three-dimensional architectures of peritoneal endometriosis, they identified two distinct main types according to the presence or absence of ramifications. The apparently multifocal occurrence in two dimensions of glandular epithelium was not confirmed by three-dimensional studies showing that all epithelial glands were interconnected by luminal structures in each peritoneal lesion. Stoval et al[24] using immunohistochemical techniques were able to detect type 1, type 3, and type 4 collagen in endometrial implants. The distribution of collagen in ectopic endometrial implants was similar to that in intrauterine endometrium from patients without endometriosis. Type 1 collagen was the predominant collagenous tissue associated with deep ectopic endometrial implants.

Attempts to classify endometriosis date back to 1949 and since the initial description over a dozen different classification systems have been proposed, the most recent of which has been the 1985 American Fertility Society

CONSIDERATIONS FOR SIMPLIFYING CHANGES OF THE REVISED AMERICAN FERTILITY SOCIETY WITH INCLUSION OF THE DEPTH OF INFILTRATION

Criteria	Depth of deepest lesion	
	Superficial (≤6mm)	Deep (>6mm)
Endometrioma absent		
Pelvic area <3cm²	Is	Id
Pelvic area >3cm²	IIs	IId
Endometrioma present		
Endometrioma <2cm³	IIIs	IIId
Endometrioma >2cm³ or bilateral endometriomas or endometriomas + dense adhesions >5cm²	IVs	IVd

From ref 25, by permission of the American Fertility Society.

revised classification. The fact that even this is now being considered for further revision (table) suggests that the perfect classification is yet to be developed. A recent classification should certainly be used in preference to an old one.

Pathophysiology

Of the troubles afflicting patients with endometriosis, pelvic pain and infertility are by far the most important. Pelvic pain probably has several origins. Of most consequence seems to be deep infiltration of endometriosis into pelvic fibromuscular tissue;[19] however, the adhesions to uterus, adnexae, bowel, and omentum undoubtedly have an important role.

The relation between endometriosis and infertility is less well understood and is felt to relate to multiple factors, including altered tubal function, folliculogenesis, peritoneal environment, and an altered immunological system that is suppressive to gametes and to fertilisation and embryo implantation.

Endometriotic implants within the fallopian tube or ovary may promote a local inflammatory response that directly harms tubal function and prevents pick-up of normal oocytes. Defective folliculogenesis seems important in reduced fertility. Reduced follicular growth, assessed by follicular diameter change, has been correlated with endometriosis.[26] Other data have also shown smaller follicles as well as lower preovulatory oestradiol values.[27] Additionally, luteinised unruptured follicle syndrome has been reported to arise more commonly in patients with endometriosis.[28] Oestradiol and progesterone concentrations in blood from peripheral and ovarian veins of women with endometriosis during early follicular phase accord with these data and have suggested an increased frequency of inadequate luteolysis and prolongation of corpus luteum function into the subsequent menstrual cycle.[29]

What is the effect on fertilisation and preimplantation embryo development? Earlier adverse reports[30,31] have been proved foundless by more recent reports of fertile women and patients with untreated endometriosis as control groups, which showed no relation between endometriosis and an increased rate of early pregnancy wastage.[32,33]

Changes in the nature and constituents of peritoneal fluid have attracted considerable attention. Halme et al[34] demonstrated increased activation of pelvic macrophages in infertile women with endometriosis, and Chacho et al[35] noted not only increased peritoneal fluid and numbers of macrophages and activated macrophages, but also a pronounced decrease in the percentage of ova penetrated in a zona-free hamster egg spermatozoa penetration assay when these macrophages were added to the assay medium. Increases in leucocytes, macrophages, helper T-cells, lymphocytes, and natural killer cells have been seen in women with stage I and stage II endometriosis.[36] Additionally, peritoneal macrophages from patients with stage I and II endometriosis have proved substantially more cytotoxic than those from healthy women. Other cytotoxic factors have also been noted (fig 2).

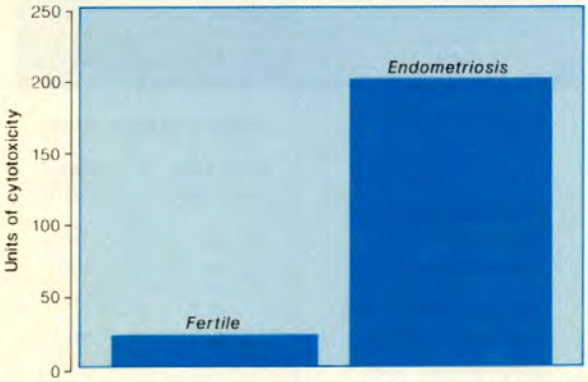

Fig 2—Tumour necrosis factor activity in peritoneal fluid of patients with (n = 34) and without (n = 16) endometriosis.

Statistical analysis based on log transformed values ($p < 0{\cdot}05$).

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Finally, prostaglandins, interleukins, and other substances produced by macrophages may be harmful to reproduction in various ways. High peritoneal-fluid prostaglandins have been related to ovulation interference as well as an increase in tubal motility, so that the embryo arrives in the uterine cavity at a suboptimum time for implantation. Fakih et al[39] demonstrated the presence of interleukin-1 in peritoneal fluid of women with endometriosis. Interleukin-1 adversely affects mouse embryo growth as well as stimulate fibroblast proliferation, collagen deposition, and fibrin formation. These data collectively suggest that changes in peritoneal environment do play an important part in the interruption of the process of normal folliculogenesis, ovulation, conception, and possible implantation.

Conclusion

The most important advances in the study of endometriosis relate not to cause and progression of the disease but to abnormalities in immunity and the peritoneal environment that result from the disease. Much is yet to be accomplished before investigators understand how endometriosis relates to the common complaints of pelvic pain and reproductive failure.

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Treatment of endometriosis

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Endometriosis is one of the commonest benign gynaecological conditions. The presenting symptoms are many and varied and, as the preceding article shows, there are numerous unanswered questions about the causation of associated symptoms. Despite these uncertainties, clinicians have had to formulate treatment approaches. There are three main goals in the treatment of endometriosis—pain relief, resolution of endometriotic deposits, and restoration of fertility, when wanted. In addition, which of several medical and surgical approaches is used is dictated by the patient's age, severity of symptoms, stage of disease, and previous response to treatment if any. The symptoms of endometriosis do not seem to be related to the extent of the disease. The occurrence of symptoms in the perimenstrual phase of the cycle is an important diagnostic pointer.

Medical treatments

Prostaglandin synthetase inhibitors

The pathophysiology of pain symptoms is unclear, but alterations in the local concentration of prostaglandins have long been suspected. Several prostaglandin synthetase inhibitors are effective in controlling dysmenorrhoea, but are less so with respect to the other components of pelvic pain in women with endometriosis.[1,2] Thus when pain is severe enough to need narcotics, hormonal suppressive treatment should be considered.

Pseudopregnancy regimens

The dependence of endometriotic tissue for its continued growth on ovarian steroid hormones,[3] especially oestrogen, has resulted in medical treatments aimed at ovarian suppression and inhibition of cyclic menstruation. Pseudopregnancy with high dose oral contraceptive pills given in a continuous, rather than cyclic, manner have generally been used. However, the efficacy of this regimen is questionable and most reports were based on uncontrolled subjective clinical trials.[4,5] They are now rarely used in established cases of endometriosis.

Progestagens

Progestagens, both those derived from progesterone (eg, medroxyprogesterone, dydrogesterone) or norethisterone (eg, norethisterone acetate and lyroestrenol) have been given in endometriosis. Progesterone can only act on endometrial cells if transformed progesterone receptors are present, themselves induced by previous oestrogen exposure. Progestagens bring about secretory changes, followed by decidual transformation, then atrophy. They also enhance the negative feedback effect of oestrogen at the

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hypothalamus with a resulting hypogonadotropic hypo-oestrogenaemic state.

In a prospective, double-blind, placebo-controlled trial the progestagen medroxyprogesterone acetate, at high dose, was as effective as danazol and significantly better than placebo in relieving pain symptoms, although dyspareunia, a frequent and distressing symptom, was not relieved.[6] Progestagens, however, seemed less effective than danazol in eliminating endometriotic deposits even when patients had little disease initially.[6]

Breakthrough bleeding is the commonest side-effect, but is usually well tolerated. Other side-effects are nausea, fluid retention, depression, and breast tenderness. Progestagens can alter lipoproteins adversely, the degree of change being related to dose and type of progestagen used. Progestagens are now frequently prescribed as agents to maintain symptomatic control after surgery or ovarian suppressive therapies.

Danazol

Danazol is an isoxazol derivative of 17α-ethinyl-testosterone and has been the preferred treatment for endometriosis for the past 15 years. The drug has multiple and diverse effects on the reproductive system. Most effects are mediated through binding to sex-hormone-binding globulin (SHBG) or to androgen receptors. One of the main biological properties of danazol is suppression of the hypothalamic-pituitary axis via decrease in frequency of gonadotropin releasing hormone (GnRH) pulses and inhibition of the mid-cycle luteinising hormone (LH) surge.[7] In the absence of gonadotropin support ovarian steroidogenesis is suppressed, with resultant low and acyclic concentrations of circulating serum oestradiol and progesterone, the degree of suppression being dose related. An effect on the immune system may also contribute to danazol's mode of action in endometriosis.

Symptomatic improvement usually begins during the first month of therapy, coincident with the onset of amenorrhoea. Subjective improvement in symptoms has been reported in 66–100% of patients and objective improvement in 51–94%;[9,12] laparoscopically assessed reduction in disease deposits has been reported in 70–94% of cases.[12,13]

The frequency and intensity of side-effects vary greatly but seem to be dose related. The most often seen side-effects are androgenic and anabolic manifestations. The appearance of androgenic side-effects depends on changes in SHBG and free testosterone concentrations and the extent of suppression of ovarian androgens. The most frequent effects are weight gain, increased appetite, acne, and oily skin; rare occurrences, which necessitate immediate cessation of therapy, are voice change and hirsutism. Exposure during pregnancy would result in masculinisation of the fetus, and contraceptive advice to prevent pregnancy during treatment is essential.

Hypo-oestrogenic manifestations—decreased breast size, hot flushes, irritability, and mood changes—can occur, but to a less pronounced extent than with GnRH analogues (table). General side-effects include muscle cramps, myalgia, oedema, rash, headaches, and alterations in liver function and lipoprotein metabolism. These side-effects are usually acceptable to patients with endometriosis in whom pain symptoms improve, but cause some to abandon treatment before completion of a full course. Reduction in total daily dose can resolve the difficulty in many cases without jeopardising clinical effect, provided that menstruation does not return.

Gestrinone

Gestrinone (13-ethyl-17α-ethinyl-17-hydroxy-gona-4, 9, 11-trien-3-one) is an anti-progestational 19-norsteroid derivative, with antigonadotropic properties, blocking the LH surge and limiting gonadotropin release. The effects of gestrinone on the endometrium include a decrease in oestrogen and progesterone receptors and induction of 17β-hydroxysteroid dehydrogenase.[14] It also has androgenic activity, although it is less pronounced than that of danazol.

Gestrinone has an elimination half-life of 28 hours and can be taken twice weekly; however, this schedule may be a disadvantage with respect to compliance. Gestrinone, like danazol, is embryotoxic and should not be taken during pregnancy. In comparative studies with danazol, gestrinone achieved similar reduction in symptoms of pelvic pain, dysmenorrhoea, and dyspareunia and regression of anatomical lesions,[15] but few follow-up data are yet available. The observed side-effects are due to the inhibition of the hypothalamic-pituitary-ovarian axis (eg, smaller breasts, decrease in libido, hot flushes) or the androgenicity of the drug (acne, hirsutism, weight gain, oedema). Gestrinone is thus a useful alternative to danazol with similar efficacy.

COMMON ADVERSE SIDE-EFFECTS IN THREE COMPARATIVE RANDOMISED TRIALS OF GnRH AGONISTS VERSUS DANAZOL

	Zoladex European trial[22]		Nafarelin European trial[24]		HRPI buserelin 310 trial[25]	
	Goserelin (3·6 mg monthly) %	Danazol (600 mg daily oral) %	Nafarelin (400 μg in) %	Danazol (600 mg daily oral) %	Buserelin (200 μg sc, 1200 μg in) %	Danazol (400–800 mg oral) %
Pain (back)	7	12	11	7	..	..
Headache	65	50	9	9	23·9	15·7
Nausea	5	12	4	5	3·4	11·8
Breast pain	5	1	11	6	..	..
Weight gain	1	27	1	38	0·9	43·1
Muscle cramps	1	12	2	8	1·7	23·5
Hot flushes	98	58	98	59	70·7	35·3
Acne	37	54	16	21	6	31·4
Oily skin/hair	25	48	..	..	..	..
Decreased libido	66	52	17	9	9·5	9·8
Vaginal dryness	71	29	18	6	29·3	7·8
Emotional instability/depression	50	44	7	5	10·3	25·5

HRPI = Hoechst-Roussell Pharmaceutical Inc; in = intranasal, sc = subcutaneous.