Association between endometriosis, dysplastic naevi and history of melanoma in women of reproductive age

Mark D. Hornstein1,6, Phaedra P. Thomas1, Arthur J. Sober2, Grace Wyshak3, Nile L. Albright4 and Rose E. Frisch5

1 Department of Obstetrics and Gynecology, Brigham and Women’s Hospital, Boston, MA 02115, 2 Department of Dermatology, Massachusetts General Hospital, Boston, MA 02114, 3 Department of Biostatistics and Department of Population and International Health, Harvard School of Public Health, Boston, MA 02115, 4 Advanced Medical Research Foundation, Boston, MA 02115 and 5 Harvard Center for Population and Development Studies, Cambridge, MA 02138, USA

6 To whom correspondence should be addressed

Women with melanoma and its precursor lesions, dysplastic naevi, have a higher prevalence of reproductive disorders than women without melanoctic lesions. This association appears strongest among young women with dysplastic naevi and endometriosis. The purpose of this study was to evaluate patients with laparoscopy-confirmed endometriosis for the presence of dysplastic naevi. A total of 66 endometriosis patients and 35 controls completed a detailed questionnaire and underwent an extensive dermatological examination for the presence of dysplastic naevi. In all, 41% of patients aged ≤32 years had dysplastic naevi, compared with 8% of controls (P = 0.038). In addition, 29% of patients with endometriosis reported a family history of melanoma compared with 10% of controls (P = 0.039). This study demonstrated an association between endometriosis and dysplastic naevi in younger women of reproductive age and found an associated family history of melanoma among endometriosis patients. These observations may be useful in the evaluation and care of young women by both gynaecologists and dermatologists.

Key words: dysplastic naevi/endometriosis/gynaecological disorders/melanoma

Introduction
Reproductive disorders and skin problems are both common in young women. Previous research has reported a higher frequency of reproductive system disorders, including benign tumours as well as more frequent endometrial biopsies and biopsies of other gynaecological organs, among women with cutaneous melanoma than among women with other skin cancers (Wyshak et al., 1989). This association may be explained by possible endocrine influences on melanoma precursors as suggested by a rise in the incidence of melanoma after puberty (Rhodes et al., 1987). Endometriosis is an oestrogen-dependent disease. Its incidence also rises sharply after puberty and is rare following menopause. Gonadotrophin-releasing hormone (GnRH) agonists decrease oestrogen concentrations and improve endometriosis-associated symptoms. It is controversial, however, whether oestrogens affect the development of melanoma (Beral et al., 1984; Gallagher et al., 1985).

A more recent study compared the frequency of reproductive disorders, including endometriosis, among 206 female patients with dysplastic naevi and/or melanoma, with their frequency among a random sample of women of comparable age without dysplastic naevi or melanoma (Frisch et al., 1992). Dysplastic naevi are considered to be both a marker for increased risk for melanoma and a melanoma precursor lesion. The highest odds ratio for these age-related skin diseases and reproductive disorders occurred among the youngest group of patients, those having dysplastic naevi alone: 44.2% (mean age 35 years) had one or more reproductive disorders, compared with 19.8% of the control sample (P < 0.001). The greatest association between dysplastic naevi and gynaecological disease was found among women with endometriosis. The prevalence of endometriosis among subjects with dysplastic naevi was 13.7% compared with 1.0% for the random sample (P = 0.001) (Frisch et al., 1992). Thus retrospective data demonstrated an association between the presence of dysplastic naevi and endometriosis. To explore this presumed relationship between endometriosis and dysplastic naevi more precisely, we evaluated patients with and without laparoscopy-confirmed endometriosis for the presence of dysplastic naevi.

Materials and methods
Between October 1992 and October 1994 a total of 139 patients of reproductive age were enrolled in this prospective study. The protocol was approved by the Human Subjects Committees of the Brigham and Women’s and the Massachusetts General Hospitals. All patients were recruited by a study nurse from the Fertility and Endocrine Unit of the Brigham and Women’s Hospital. The recruiter was unaware of subjects’ medical history upon enrolment in the study. Women of reproductive age who had undergone a laparoscopy or laparotomy for endometriosis, pelvic pain, or infertility within the 24 months of the study were included. The surgical operative reports from the Brigham and Women’s and referring hospitals and patient histories were reviewed to confirm the absence or presence of endometriosis. Endometriosis was diagnosed by surgical inspection including atypical lesions (Jansen and Russell, 1986) or by pathology. Study participants were administered a short questionnaire, which included demographic and gynaecological data, and specific questions about family history of endometriosis and melanoma. All participants underwent a dermatological examination performed by the same staff dermatologist (A.J.S.) at the Massachusetts General Hospital to determine the presence, number, and location of dysplastic naevi and melanomas. The
Dysplastic naevi were histologically or clinically confirmed according to previously published histological and clinical criteria (Elder et al., 1982; Rhodes et al., 1989). Patients were classified as having histologically confirmed dysplastic naevi if at least one excised lesion had melanocytic atypia and/or architectural features of a dysplastic naevus. Patients were classified as having clinically confirmed dysplastic naevi if the naevi were >5 mm in diameter and had an indistinct border, a target or fried egg shape or a variegated pigmentation pattern. Patients were classified as possibly having dysplastic naevi if the lesion was >5 mm in diameter but lacked other criteria to confirm the diagnosis as dysplastic naevi. Histology was not confirmed in all cases as it no longer represents the 'gold' standard for the diagnosis of dysplastic naevi (NIH, 1992).

Of the 139 patients enrolled, 34 did not undergo the dermatological evaluation and were eliminated from the study. In addition, diagnosis could not be confirmed or was unclear on surgical reports for four patients who indicated on the questionnaire that they had endometriosis. These patients were also excluded from the analysis. Of the 101 remaining patients, 66 had surgically proven endometriosis (57 at laparoscopy and nine at laparotomy), and 35 patients without endometriosis were controls. More endometriosis patients than controls expressed interest in participating in the study leading to an approximately 2:1 ratio of cases to controls. Among endometriosis patients, 18 had stage I disease, nine had stage II, 13 had stage III and 9 had stage IV using the American Fertility Society Classification (American Fertility Society, 1995). In 17 patients, the surgeon did not identify the stage of the disease. Among control women, pelvic adhesions without endometriosis was the most common diagnosis at surgery (13 patients), followed by normal pelvis (10 patients), fibroids (six patients) and other diagnoses (six patients).

Statistical methods included Student’s t-tests (two-tailed) for continuous variables, and χ² and odds ratios for categorical data. The analysis was performed using the Statistical Analysis System (SAS) for personal computers. The results are reported as mean ± SD or as percentages where appropriate. Differences were considered to be statistically significantly different when P < 0.05.

Results
The characteristics of the 66 patients with endometriosis and the 35 controls are shown in Table I. The mean age of the endometriosis patients at study entry was 32.0 ± 5.9 years; for the controls, 34.7 ± 5.6 years (P < 0.05). The mean number of pregnancies was higher among controls, as expected, than among the endometriosis patients, who have a high incidence of infertility. Other personal characteristics such as weight, height, and age of menarche did not differ significantly between the two groups. Medical conditions and family history of endometriosis also did not differ significantly between the two groups (Table I). The odds ratio among all study subjects for the association between endometriosis and dysplastic naevi (one or more versus none) was 1.7 [95% confidence intervals; (0.7, 4.3), P = 0.27]. Because the women with endometriosis were significantly younger, and on the basis of findings in younger reproductive-age women reported previously (Wyshak et al., 1989), the data were stratified post hoc by the median age of the population (32 years). Among those 32 years or younger, 41.0% of endometriosis patients had dysplastic naevi versus only 8.3% of controls (P = 0.038) (Table Ia). Among women >32 years, 22.2% of endometriosis patients had dysplastic naevi versus 30.4% of controls (P = 0.514) (Table Ib). Subjects were also asked about a family history of melanoma. Among endometriosis patients 14 of 49 (28.6%) had a family history of melanoma, while among non-endometriosis patients three of 30 (P = 0.039) gave a similar history. Not included in the comparison were 22 women who did not know whether they had a family history of melanoma. Of these, 17 (77%) had endometriosis and five (23%) did not.

Discussion
The major finding of this study is an association between endometriosis and dysplastic naevi in women ≤32 years of age of the population (32 years). Among those 32 years or younger reproductive-age women reported previously (Wyshak et al., 1989), the data were stratified post hoc by the median age of the population (32 years). The major finding of this study is an association between endometriosis and dysplastic naevi.
age. Although this association did not pertain for the entire patient population, it is notable that in a previous study (Frisch et al., 1992), the dysplastic naevis patients without melanoma were the youngest of the patient groups. This group also had the largest number of gynaecological disorders compared with the random sample of similar age.

The finding of a higher prevalence of dysplastic naevi in younger women may be due to greater sun exposure earlier in life in individuals at greater risk for melanotic skin disease. In addition, this study found a positive association between a family history of melanoma and the presence of endometriosis. Both diseases have strong familial components. Patients with endometriosis are seven times more likely to have a first-degree relative who has endometriosis than a more distant relative (Simpson et al., 1980). Additionally, Kennedy et al. recently reported a similar age of onset of pain symptoms in non-twin sisters with endometriosis, suggesting a genetic basis for the disease. Thus, one might speculate that the gene or genes that predispose women to both diseases may be related or segregate together during meiosis. A gene for melanoma has been localized on the short arm of chromosome 9 (9p21) in a region close to the locus for galactose-1-phosphate uridyl transferase (GALT), an enzyme important in galactose metabolism (Fountain et al., 1993). Women with endometriosis and their mothers have recently been found to have a higher frequency of mutations of the GALT gene than the general population (Cramer et al., 1996), again suggesting a possible genetic linkage between endometriosis and melanoma.

The explanation for the observed association between endometriosis and the premalignant skin condition, dysplastic naevi, is uncertain and may merely represent an epiphenomenon for a co-factor such as infertility; however, some interesting observations may be relevant. Immune mechanisms have also been suggested as important in the pathogenesis of endometriosis (Evers, 1992). In addition, decreased natural killer (NK) cell activity has been identified in the pelvis of women with endometriosis (Oosterlynck et al., 1991), and immune dysfunction has been observed in melanoma-prone families (Dean et al., 1979). Low NK cell activity in familial melanoma patients and their relatives, apparently without other deficiencies in immune function, has also been reported (Hersey et al., 1979).

In a study of this type some potential sources of bias are unavoidable. For example, some study subjects did not know whether or not they had a family history of melanoma and therefore could not be included in that analysis. It is possible that endometriosis patients may better recall their family medical history. In general, cases tend to recall more medical history than controls so if a bias did exist it would most likely further increase rather than decrease the statistical significance of the association seen. The inclusion of patients with pelvic adhesions in the control group could potentially include those whose source of adhesions was endometriosis but in whom endometriosis was not seen at surgery. Such a bias would tend to decrease the magnitude of the association, since cases of endometriosis would have been included in the control group.

In summary, this study has demonstrated an association between endometriosis and dysplastic naevi in younger women of reproductive age and an associated family history of melanoma in endometriosis patients. Clinicians both in dermatology and gynaecology can use this information when treating patients with either condition until additional studies further delineate the association between these common diseases among reproductive-age women.

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