

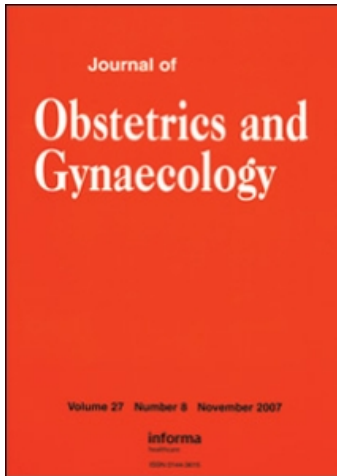
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Uterine innervation in fibroids: A qualitative study

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Summary

This study describes the innervation of uterine fibroids in a retrospective survey of archived material. A total of 24 uteri containing fibroids were identified; four nulliparous uteri with single large fundal fibroids (200–320 g) and 20 multiparous uteri with one, or more, fibroids (80–230 g). Tissue blocks from the uterine isthmus and the fibroids, were identified, sectioned and stained for nerves with anti-S100 using a standard immunohistochemical regimen. Normal uterine innervation includes concentrations of nerves in the subserosal layer and at the endometrial-myometrial interface with sparse neurovascular bundles distributed throughout the myometrial stroma. Nulliparous uteri with single large fibroids demonstrated relatively normal patterns of innervation with nerves distributed throughout the stroma of the fibroid. In multiparous uteri with fibroids, there were no nerves detectable in the substance of the fibroids. Increased numbers of nerve fibres were observed in the pseudo-capsule of some fibroids and may reflect compression of normal myometrial tissue and their contained nerves, or, a minor degree of nerve fibre proliferation. This study demonstrates that fibroids in multiparous uteri do not contain nerves. Single, large nulliparous fibroids situated at the uterine fundus appear to contain relatively normal patterns of innervation.

Keywords

Uterus, nerves, innervation, fibroids, leiomyomas

Background

Uterine fibroids occur in 5–77% of women depending on the method of diagnosis (Wallach and Vlahos 2004). They may be single or multiple, vary considerably in size, and, account for approximately one-third of hysterectomies (Wilcox et al. 1994; Gambone et al. 1990). Their aetiology remains unknown, though a number of risk factors and growth promoters have been identified (Flake et al. 2003).

Early menarche, nulliparity, black race, increasing age within the reproductive years, obesity and diet increase the risk for fibroids (Flake et al. 2003). Several studies have demonstrated an excessive risk with increasing body mass index; specifically a 21% increase in risk for each 10 kg of body weight (Ross et al. 1986). In one study of women undergoing hysterectomy for fibroids, 51% were overweight and 16% were severely obese (Shikora et al. 1991). The apparent association between fibroids and obesity has been attributed to hormonal factors that contribute to excessive circulating oestrogens. Diet may contribute to these effects, in that a modest association was found between fibroids and the consumption of beef and ham, whereas a high intake of green vegetables appeared to be protective (Chiaffarino et al. 1999).

Promoters of fibroid growth include altered levels of oestrogen, increased numbers of oestrogen receptors and predisposing genetic factors. An increased incidence in first degree relatives has been described in two Russian studies (Vikhlyayeva et al. 1995; Kurbanova et al. 1989), and, also in a study from Washington where the odds ratio increased to 5.7 for early-onset fibroids (Schwartz et al. 2000). Many cytogenetic associations have been proposed, including deletion of chromosome 7 trisomy 12, and rearrangements

of the short arm of chromosome 6 (Nilbert and Helm 1990; Ligon and Morton 2001). No clear view regarding the aetiology of fibroids has been developed despite the detailed knowledge of risk factors and promoters for their growth and development. This question has been approached in this study by examining the innervation of fibroids following hysterectomy for a variety of benign indications.

Materials and methods

Uteri containing fibroids were identified retrospectively from the histopathology archive. Histology reports describing significant co-existent pathology, such as adenomyosis or endometriosis were not included in this study. Four, premenopausal nulliparous uteri containing single, large fundal fibroids (200–320 g) were identified in the tissue archive. No co-existing pathology was identified on the report or the available blocks. A total of 20 premenopausal multiparous uteri following hysterectomy (80–230 g) for benign conditions in premenopausal, parous women were also identified. Sections were cut and stained with anti-S100 as described below. Ethical approval for this study was obtained from the Local Research Ethics Committee.

Tissue sections were stained with anti-S100 (Dako Z0311; DakoCytomation A/S) using a standard immunohistochemical regimen. Paraffin sections (3 µm) were dried, de-waxed and rehydrated. De-paraffinised sections were pretreated with trypsin (Difco 215230, DakoCytomation A/S, Glostrup, Denmark) before polyclonal anti-S100 protein (Dako Z0311; DakoCytomation A/S) was applied. Endogenous peroxidase activity was eliminated by the application of a commercial peroxidase blocking solution

(Dako S2023). Sections were stained on an automated immunohistochemical stainer with detection kit (Dako K5001; ChemMate TM; Dako-Cytomation A/S. The nuclei were counterstained with haematoxylin. Sections of pancreas were used as positive controls and incubated on all slides throughout the staining procedures.

Results

Normal patterns of myometrial innervation were observed in both nulliparous and multiparous uteri with

concentrations of nerves at the endometrial-myometrial interface and in the subserosal layers (Figure 1). Relatively sparse innervation was observed through the remainder of myometrium except in some of parous uteri where there were occasional circumscribed areas of nerve fibre proliferation in the myometrial stroma (Quinn and Kirk 2002).

In parous uteri, no nerves were observed in fibroids irrespective of the number and dimensions of the tumour (Figures 2–3). There appeared to be slightly increased numbers of nerve fibre profiles in the pseudocapsules of some fibroids (Figure 4), though whether these were

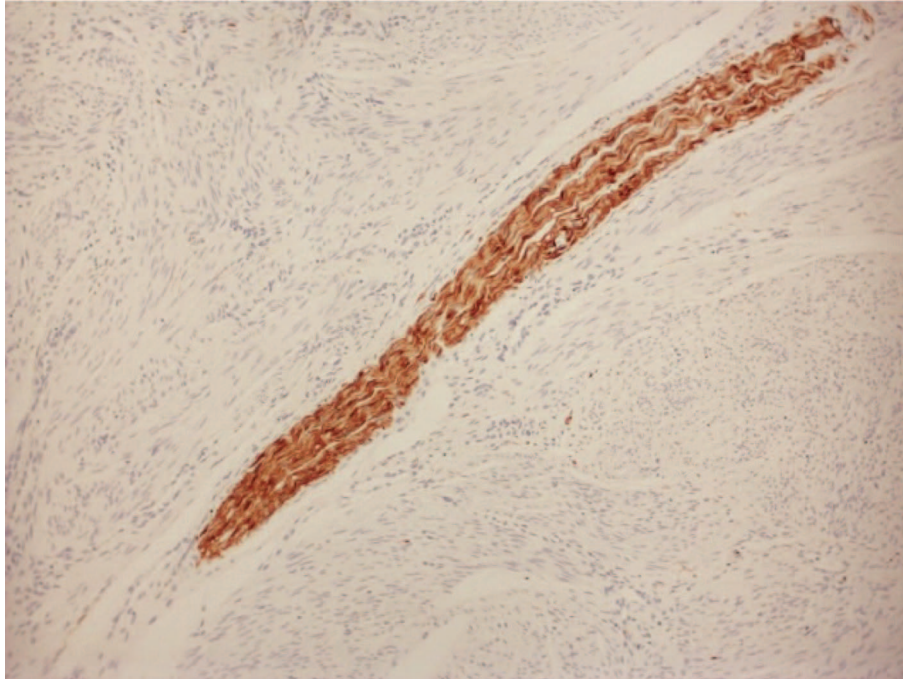


Figure 1. Normal myometrium is sparsely innervated with occasional nerve bundles and their branches (anti-S100, magnification $\times 20$).



Figure 2. Small fibroids carry no nerves. The body of the fibroid is devoid of neural tissue (magnification $\times 20$).



Figure 3. The same field as Figure 2, under low power (magnification $\times 10$).

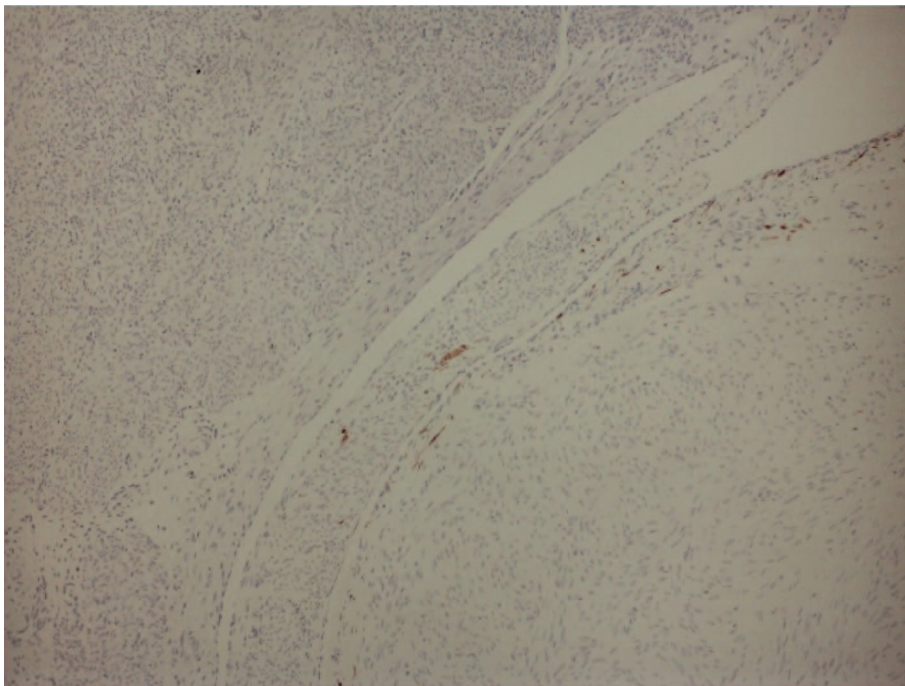


Figure 4. The 'pseudocapsule' of the fibroid demonstrates minor increases in nerve fibre profiles (magnification $\times 10$).

associated with compression of normal myometrium or minor degrees of nerve fibre proliferation, was not apparent. In large, nulliparous, fundal fibroids there were relatively normal patterns of innervation in both the myometrium and throughout the fibroid (Figure 1).

Discussion

Absence of innervation has been observed in leiomyomas in premenopausal, parous uteri. Similar observations have been previously noted in the Russian literature without

suggesting any possible relationship with parity (Savitskii et al. 1981, 1986). Sampson (1912) reported that small fibroids were usually less vascular than the surrounding myometrium, whereas the vascularity of large fibroids was typically greater than that of the surrounding myometrium. These observations have been confirmed by recent studies using more sophisticated techniques though a coherent explanation has not been advanced (Casey et al. 2000). Such studies have not drawn attention to the possible aetiological distinction between large, nulliparous, fundal fibroids and multiple, smaller, parous fibroids described in this study.

Absence of nerves in proliferating endometrium and loss of nerves at the endometrial-myometrial interface have been observed in adenomyosis (Quinn and Kirk 2002; Quinn 2007). In some cases, nerve fibre proliferation was observed outside the columns of proliferating endometrium. Uteri with co-existing adenomyosis and fibroids were excluded from this study, though the present observations suggest the possibility that neural injuries may contribute to the aetiology of both conditions. Injuries to the endometrial-myometrial nerve plexus may contribute to the development of different patterns of adenomyosis and submucosal fibroids. Uterine nerves may be injured during vaginal delivery, constipation and some patterns of surgery (Quinn and Kirk 2002; Quinn and Armstrong 2004; Atwel et al. 2005).

Injuries to individual nerves may release a localised area of myometrium from negative trophic control resulting in localised myometrial proliferation with subsequent growth promotion through oestrogen. For example, perforation of the uterine fundus may lead to the development of a single, large, intracavitary fibroid through such a mechanism, though this would be of relatively uncommon origin compared with possible intrapartum injuries. Minor increases in nerve fibre numbers in the 'pseudocapsule' may represent minor neural proliferation or compression of normal myometrial nerves. Congenital problems with fusion of the two halves of the uterus may create the circumstances for localised myometrial proliferation at the fundus in the nulliparous uterus as opposed to variable injuries to uterine innervation in the parous uteri described in this study.

Prospective quantitative studies of uterine innervation would be helpful to confirm these observations as well as identifying possible obstetric injuries to account for any putative intramyometrial injury. The site, nature and extent of injury to the uterine innervation may result in different benign uterine pathology with an extrinsic neural injury resulting in nerve fibre proliferation in the isthmus accounting for some of the symptoms of endometriosis (Atwel et al. 2005); intrinsic neural injury at the endometrial-myometrial interface resulting in adenomyosis (Quinn and Kirk 2002; Quinn 2007), and localised injuries to nerves in the myometrium being the source of myometrial proliferation in parous fibroids.

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