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REVIEW

Is fibroid heterogeneity a significant issue for clinicians and researchers?

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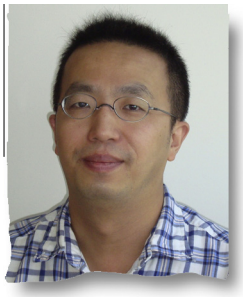

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Abstract The clinical and scientific literature overwhelmingly deals with fibroids as a single entity or disease. This convenient assumption of homogeneity may be an important oversight given that substantial evidence exists for heterogeneity between fibroids at many levels. Failure to recognize and accommodate fibroid heterogeneity can have significant ramifications for both clinical treatment decisions and research protocol design. The aim of this article is to review the current knowledge of fibroid heterogeneity and to identify key areas where fibroid heterogeneity should be taken into consideration both clinically and when designing research protocols. Uterine leiomyomata display significant and well-documented heterogeneity in symptoms, diagnostic imaging appearance, pathology, genetic background and therapeutic requirements. Additional research is needed to better understand fibroid heterogeneity as it relates to pathogenesis, molecular targets for potential new therapies, patient symptoms and, ultimately, treatment. To this list should also be added heterogeneity of genetics, lifestyle and individual clinical characteristics of the fibroid. Increasingly, an understanding of uterine leiomyoma heterogeneity will be of importance for clinicians who see patients with this common and costly disease.

KEYWORDS: genetics, heterogeneity, pathogenesis, therapy, uterine leiomyoma

Introduction

Uterine leiomyomata, or fibroids, are benign myometrial neoplasms that are typically enriched in extracellular matrix (Stewart, 2001). They are a common tumour, occurring in up to 77% of women of reproductive age (Cramer and Patel, 1990). Among women of African descent, there is an even higher incidence (Baird et al., 2003; Marshall et al., 1997), with African Americans experiencing more severe symptoms, presenting with larger tumours and having a 3-fold higher risk of hysterectomy than American whites (Kjerulff et al., 1996).

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Uterine leiomyomata are a significant cause of reproductive and gynaecological problems, including heavy menstrual bleeding, chronic pelvic pain, dysmenorrhoea, infertility, recurrent miscarriage, preterm delivery and post-partum haemorrhage (Flake et al., 2003; Stewart, 2001) Uterine fibroids are the primary indication for hysterectomy, with over 200,000 such procedures performed annually on US women (Farquhar and Steiner, 2002). Figures from the USA based on year 2000 data calculate an estimated annual direct healthcare cost for fibroids of US$ 2.15 billion (Flynn et al., 2006). There are approximately 400,000 new cases diagnosed each year for US women of all races aged 25–44 (Hartmann et al., 2006).

The clinical and scientific literature overwhelmingly deals with fibroids as a single entity or disease. This convenient assumption of homogeneity may be an important oversight given that substantial evidence exists for heterogeneity between fibroids at many levels, including aetiology, symptoms and pathogenesis (Peddada et al., 2008; Walker and Stewart, 2005). Failure to recognize and accommodate fibroid heterogeneity can have significant ramifications for both clinical treatment decisions and research protocol design. This in turn will hinder progress in understanding the pathogenesis and developing new treatments for this common and costly disease.

The aim of this article is to review current knowledge of fibroid heterogeneity and to identify key areas where fibroid heterogeneity should be taken into consideration both clinically and when designing research protocols.

Symptoms

Uterine leiomyomata are asymptomatic in at least 50% of afflicted women (Divakar, 2008; Gupta et al., 2008; Levy, 2008), while other studies estimate that only 20–25% of women with leiomyomata are symptomatic (Babaknia et al., 1978; Buttram and Reiter, 1981; Cramer and Patel, 1990; Hunt and Wallach, 1974). Symptoms are more likely to occur with large fibroids, multiple fibroids or fibroids at specific locations and tend to alleviate after the menopause. The common symptoms of fibroids can be divided into three major categories: abnormal bleeding, pelvic pressure and pain, and problems with fertility and pregnancy.

Abnormal uterine bleeding

Approximately 30% of women with leiomyomata have been reported to have menstrual abnormalities such as heavy menstrual bleeding and prolonged bleeding (Buttram and Reiter, 1981). Anaemia is often present in association with heavy menstrual bleeding. The incidence of heavy menstrual bleeding increases as women reach their perimenopausal years (Wilcox et al., 1994). It is difficult to determine whether heavy menstrual bleeding in perimenopausal patients is attributable to fibroids because at this time dysfunctional uterine bleeding also increases. To establish whether leiomyomata are the cause of heavy menstrual bleeding, the assessment of menstrual loss should ideally be objective, because patients may underestimate or overestimate their blood loss. Rybo et al. (1985) conducted an objective study and found that 40% of women who bled greater than 200 ml each period had leiomyomata; in comparison, only 10% of those who bled 80–100 ml had leiomyomata. A population-based study by Marino et al. (2004) found no association between menstrual loss and uterine leiomyomata. Since around three-quarters of women over the age of 40–45 have leiomyomata and the majority of women are asymptomatic, it is likely the sample size would need to be much larger to see a difference in a population-based study.

Increased uterine bleeding is often attributed to the encroachment of one or more submucosal leiomyomata (Bukulmez and Doody, 2006; Hickey and Farquhar, 2003; Kelly and Cullen, 1909). The review by Lumsden (1998) found that only 40% of those having a hysterectomy for heavy menstrual bleeding had submucosal leiomyomata. A randomized study suggested that non-submucosal leiomyomata were associated with essentially the same increase in heavy bleeding as submuscosal leiomyomata of similar size (Wegienka et al., 2003). This observation supports the idea that the mechanisms by which some leiomyomata cause heavy menstrual bleeding are complex and heterogeneous. Theories proposed to account for fibroid-related heavy menstrual bleeding include reduced myometrial contractility, increased endometrial surface area and dilated vessels overlying the leiomyomata (Farrer-Brown et al., 1970; Lefebvre et al., 2003), abnormal vessel structure (Buttram and Reiter, 1981; Farrer-Brown et al., 1971) and differential growth factor expression (Chandrasekhar et al., 1992; Harrison-Woolrych et al., 1994; Mangrulkar et al., 1995; Vollenhoven et al., 1993).

Apart from heavy menstrual bleeding, prolonged vaginal bleeding is another common bleeding symptom, although relatively little has been published on this topic in relation to fibroids. Wegienka et al. (2003) did not find an association between the length of menstruation and leiomyomata. Other abnormal bleeding symptoms include frequent bleeding and intermenstrual bleeding or spotting.

Pressure symptoms and pain

Leiomyomata of different locations may cause urinary frequency, urinary retention, ureteric obstruction or constipation (Gupta et al., 2008; Kelly and Cullen, 1909). However, there are very few reports that objectively evaluate the evidence for leiomyomata causing pressure symptoms (Farquhar et al., 2001).

A pedunculated subserous leiomyomata may undergo torsion or a submucosal leiomyomata prolapse through the cervix may cause acute pain. Red degeneration in pregnancy can also be associated with pelvic pain, although another study failed to find correlation between symptoms and the histological finding of degeneration (Candiani et al., 1990). A population-based study also found no association between leiomyomata and dysmenorrhoea (Lippman et al., 2003). As for abnormal bleeding symptoms, there is significant heterogeneity in pressure and pain symptoms between fibroids, with the majority being asymptomatic.

Reproductive problems

To date, there has been no randomized clinical trial to address whether leiomyomata are a cause of infertility