

## Uterine fibroids

*Elizabeth A. Stewart<sup>1</sup>, Shannon K. Laughlin-Tommaso<sup>1</sup>, William H. Catherino<sup>2</sup>, Sujata Lalitkumar<sup>3</sup>, Devashana Gupta<sup>4–6</sup> and Beverley Vollenhoven<sup>4–6</sup>*

**Abstract** | Uterine fibroids (also known as leiomyomas or myomas) are common clonal neoplasms of the uterus. Fibroids have both smooth muscle and fibroblast components, in addition to a substantial amount of fibrous extracellular matrix, which all contribute to the pathogenetic process. Fibroids are extremely heterogeneous in their pathophysiology, size, location and clinical symptomatology. They are also a part of a range of disease in which some variants have facets of malignant behaviour but overall are benign. Risk for fibroids is associated with race; black women have a higher risk of developing fibroids earlier in life than their white counterparts and also develop more-severe forms of the disease. Clinically, fibroids account for one-third to half of all hysterectomies and are associated with substantial morbidity and health care costs for women of reproductive age. Indeed, current treatments are primarily surgical and interventional; approximately three-quarters of all fibroid treatments are hysterectomies. However, clinical innovations are emerging in the use of progesterone receptor modulators as a medical therapy. New information is rapidly accumulating about the genetic subgroups that lead to fibroid formation, which might aid further understanding of the clinical heterogeneity of this disease and lead to individualized treatments. This information is a crucial development given the current lack of high-quality evidence on which to base therapeutic decisions.

Uterine fibroids (also known as leiomyomas and myomas) are benign lesions or neoplasms of the uterus that are composed of smooth muscle cells and fibroblasts and are rich in extracellular matrix (ECM). Fibroids seem to develop and regulate gene expression in response to the menstrual cyclicity of gonadal steroids (mainly oestrogen and progesterone) and develop between menarche and menopause<sup>1</sup>.

Fibroids are a major source of morbidity for women of reproductive age. They can cause heavy or prolonged menstrual bleeding that can lead to social embarrassment and, frequently, the development of iron-deficiency anaemia. Fibroids can also enlarge the uterus and can lead to urinary symptoms (such as frequent urination, nocturia or urinary retention) or gastrointestinal symptoms (such as diarrhoea or constipation), in addition to abdominal distension or pain. However, women can remain asymptomatic, even with large fibroids.

The morbidity of fibroids is further underscored by its main treatment option, hysterectomy, a major surgery that eliminates the risk of childbearing and has profound consequences for general health. In the United States, the lifetime risk of hysterectomy is 45%<sup>2</sup>. Whereas only 8% of hysterectomies are performed for any type of cancer treatment, globally, fibroids contribute to at least one-third and up to half of all hysterectomies. Hysterectomy

still accounts for almost 75% of all fibroid-related surgeries in populations in the United States, despite an increasing array of alternative therapies<sup>3</sup>.

Treatment of fibroids also extends beyond hysterectomy. Other treatments include various surgical procedures to extirpate the fibroids (such as myomectomies and the surgical excision of fibroids), embolization procedures and a range of thermoablative therapies. In addition, several medical therapies can be used for the treatment of fibroids or their associated heavy menstrual bleeding — such as progesterone receptor modulators (PRMs), tranexamic acid, gonadotropin-releasing hormone (GnRH) agonists — and others that provide symptomatic relief (mainly oral contraceptives and the levonorgestrel intrauterine device).

In addition to health care expenses, the indirect costs of fibroids, such as loss of monetary income caused by time out of work and disability, accounts for a substantial proportion of the total costs of this disease<sup>4</sup>. Furthermore, added costs of sanitary products, over-the-counter remedies, alternative and complementary therapies and adult diapers for women with the heaviest menstrual bleeding are typically not taken into account. Fibroids are also associated with infertility and other pregnancy complications, which also contribute to the costs and morbidity.

Correspondence to E.A.S.  
Departments of Obstetrics  
and Gynecology and Surgery,  
Mayo Clinic, 200 First  
Street SW, Rochester,  
Minnesota 55905, USA.  
[stewart.elizabeth@mayo.edu](mailto:stewart.elizabeth@mayo.edu)

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**Author addresses**

- <sup>1</sup>Departments of Obstetrics and Gynecology and Surgery, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA.
- <sup>2</sup>Department of Obstetrics and Gynecology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA.
- <sup>3</sup>Department of Obstetrics and Gynecology, Karolinska Institutet, Stockholm, Sweden.
- <sup>4</sup>Department of Obstetrics and Gynecology, Monash University, Clayton, Victoria, Australia.
- <sup>5</sup>Women's Program, Monash Health, Melbourne, Victoria, Australia.
- <sup>6</sup>Monash IVF, Clayton, Victoria, Australia.

Fibroids have an interesting biology, which has been understudied. Paradoxically, fibroids can increase in volume by up to 138% in 6 months but have a low mitotic index<sup>5</sup>. The ECM contributes to growth factor sequestration and solid-state signalling in fibroids, rendering the neoplasms stiff. However, the relative contributions of the cellular compartment versus the ECM in growth of the neoplasm are not well understood. Moreover, there are hypotheses but little evidence about how fibroids cause prolonged or heavy menstrual bleeding<sup>6</sup>. In addition, the size of fibroids is impressive; a 10–20 cm lesion is not uncommon (FIG. 1). Whether fibroids can escape clinical detection by staying ‘hidden’ in the pelvis or owing to an underlying feature of their regulated growth remains unclear.

Fibroids are also part of a range of disease in which rare variants manifest some facets of malignancy but are overall benign<sup>1</sup>. For example, benign metastasizing leiomyomas can be found in distant sites, such as the lungs, but can be histologically benign and stable over long periods of time. Intravenous leiomyomas can spread contiguously from the uterus through the vascular tree to the heart, but do not invade other tissues. Disseminated peritoneal leiomyomatosis can spread in a miliary manner throughout the peritoneum, similar to an ovarian or primary peritoneal tumour, but has a benign microscopic appearance and no tissue invasion.

Fibroids are common and large, facilitating the easy acquisition of tissue for research. Fibroids are also a good model system for testing minimally invasive therapies that could subsequently be used to treat malignant tumours; they are easy to target, have discrete borders and the consequences of incomplete therapy are minimal. This Primer reviews the epidemiology, pathophysiology and management of uterine fibroids and discusses the key unanswered research questions regarding this disease.

### Epidemiology

Fibroids are common and occur in >70% of women based on data from ultrasonography-screening studies and pathology data<sup>7,8</sup>. However, fibroids can be asymptomatic, with clinical symptoms reported in 25–50% of women. Self-reported rates of clinical diagnoses (which include the more-severe cases that lead to hysterectomy) offer estimates of women affected by

the symptoms of fibroids. These estimates range from 12.8 per 1,000 person-years for self-reported diagnoses to 2 per 1,000 person-years for hysterectomy-confirmed cases in the United States<sup>9</sup>. In a European survey, the prevalence of diagnosed symptomatic fibroids ranged from 11% in France to 24% in Italy<sup>10</sup>. It is likely that women experience fibroid symptoms for several years before being diagnosed<sup>11</sup>.

The main risk factors for fibroids include age and race. Fibroids have not been described in pre-pubertal girls, but can start to develop during teenage years<sup>12,13</sup>, after which incidence rises until menopause<sup>14</sup>. Prevalence and incidence differ for white and black women for unknown reasons (FIG. 2); the incidence of fibroids is two to three-times greater among black women than white women after accounting for age and other risk factors in populations in the United States<sup>8,9</sup>. In addition, the prevalence of both self-reported and ultrasound-detected fibroids was higher among black women than white women<sup>15</sup>. In an ultrasonography-screening study in the United States, black women developed fibroids approximately 10 years earlier than white women; the incidence of fibroids sharply inclined around 25 years of age for black women and 35 years of age for white women, and reached a peak prevalence of 80% and 70%, respectively, by 50 years of age<sup>8,12</sup>. When restricted to clinically significant fibroids (defined as a uterus size equivalent to or greater than that of a uterus at 9 weeks of gestation, at least one fibroid of ≥4 cm in size and/or one or more submucosal fibroid), estimates of point prevalence were 50% for black women and 25% for white women<sup>8</sup>. Moreover, the severity of fibroid symptoms tends to be greater among black women than white women. Black women with fibroids have larger uteri, more fibroids and larger fibroids than white women; fibroids in black women also do not show decelerated growth as the women approach menopause, as fibroids in white women do<sup>5</sup>. In the United States, mean ages at hysterectomy were lower among black women than white women and black women were seven-times more likely to undergo a myomectomy than white women<sup>16</sup>. In a hysterectomy-based study<sup>17</sup> in South Africa, black women were 20% more likely to have histological evidence of fibroids than women of white, Indian or mixed descent. Genetic studies suggest that fibroids might be linked to having a greater component of African than European ancestry<sup>18,19</sup>. Data on fibroid incidence among Asian and Latin American women in the United States are limited but seem to be closer to the rates among white women<sup>9,12</sup>.

Parity also influences fibroid development and growth; women who have pregnancies that are >20 weeks have decreased risk of developing fibroids. Specifically, uterine remodelling after pregnancy has been hypothesized to help shrink or eliminate fibroids<sup>8</sup>. In women with a solitary fibroid in early pregnancy, this fibroid was no longer detectable via imaging in 36% of women after giving birth, and of the remaining tumours, 80% were smaller postpartum<sup>20</sup>. Other hormonal risk factors include early age at menarche (<10 years of age) and prenatal exposure to

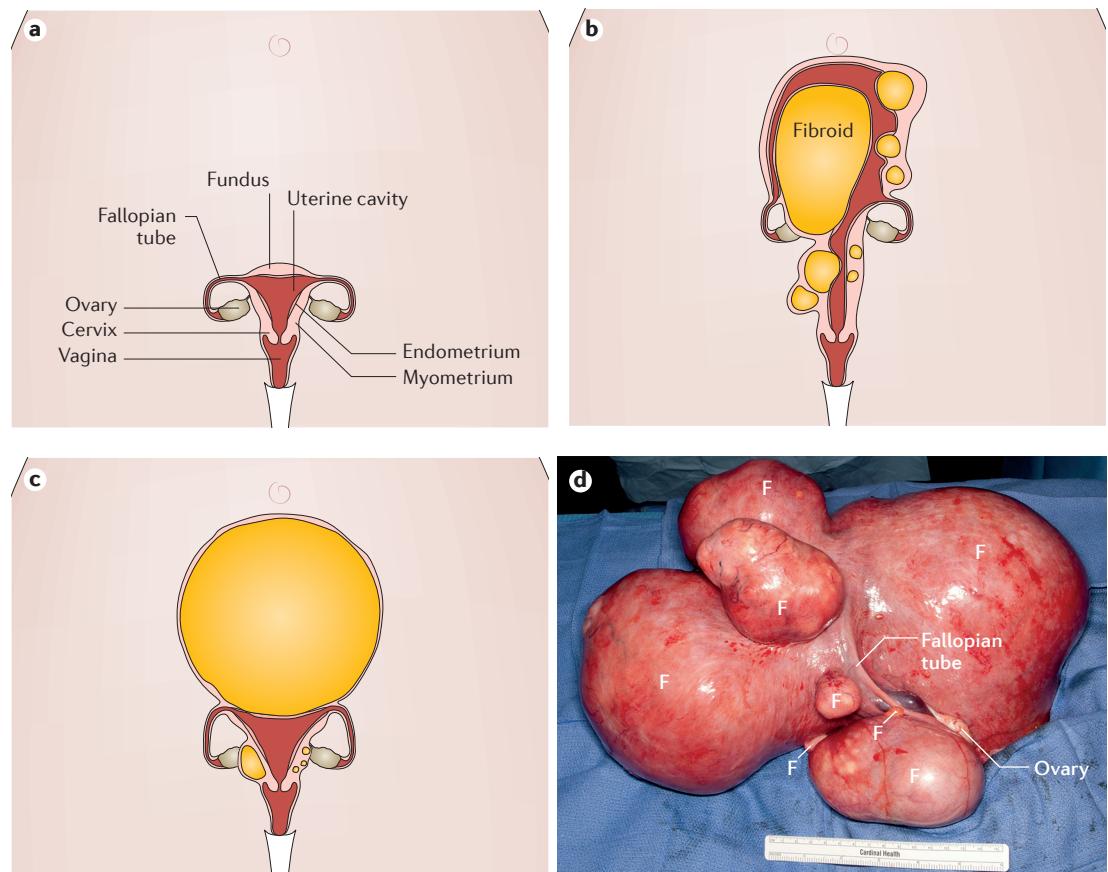
diethylstilbestrol — a non-steroidal oestrogen analogue<sup>21,22</sup>. Exposure to long-acting progestins, such as depot medroxyprogesterone, decreases the risk of fibroids<sup>23,24</sup>. The use of oral contraceptives does not affect the development or growth of fibroids<sup>24</sup> except possibly when used before 16 years of age<sup>25</sup>.

Dietary factors have also been associated with the risk of developing fibroids. A diet heavy in red meat is associated with a 70% increased risk of fibroids, whereas green vegetable and fruit intake reduces the risk<sup>26</sup>. Dairy consumption decreases the risk of fibroids in a dose-response manner; women who reported consuming ≥4 servings of dairy per day had a 33% decrease in the risk of fibroids compared with women who consumed <1 serving per day<sup>27</sup>. This finding is particularly interesting given the higher likelihood of lactose intolerance in black women. Soy intake, often a substitute for dairy, was not associated with fibroid risk. Alcohol consumption, especially beer, increased the risk of fibroids. Vitamin D deficiency, which is more common in women of African descent than in white women<sup>28,29</sup>, has been associated with an increased risk of fibroids and has also been theorized to explain some of the differences in fibroid prevalence between black and white women<sup>30</sup>.

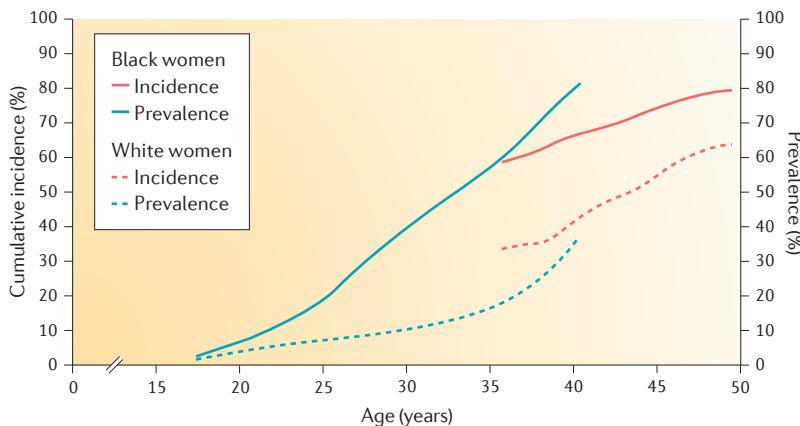
Other factors potentially associated with fibroids include sexually transmitted infections. A large prospective study (the SELF trial) is investigating the associations between sexually transmitted infections and fibroids observed in prior studies. In baseline analyses, this trial did not confirm the increased risk of fibroids with pelvic inflammatory disease but supported the increased risk of fibroids in women with a history of bacterial vaginosis<sup>30–32</sup>. Data from prospective serological and vaginal bacterial analyses are currently pending in the SELF trial. In a cross-sectional study, immunostaining of fixed fibroid tissue did not reveal the presence of latent *Chlamydia* spp.<sup>31</sup> or herpes simplex viruses. Interestingly, an inverse relationship between fibroids and abnormal pap tests has been reported in three cohorts<sup>31–33</sup>, indicating a possible protective effect of the human papillomavirus on fibroids.

### Mechanisms/pathophysiology

The traditional definition of uterine fibroids is that they are clonal smooth muscle cell neoplasms that are growth-responsive to gonadal steroids and have characteristic chromosomal rearrangements underlying their development. Research continues to expand this concept but has confirmed some of the key constituents (FIG. 3).



**Figure 1 | The heterogeneity of fibroid disease.** **a** | Normal uterine anatomy. **b** | A uterus the size of a uterus at 20 weeks of gestation that contains multiple fibroids (F), resulting in distortion and elongation of the endometrial cavity. **c** | In this uterus, also the size of a uterus at 20 weeks of gestation, the large fundal fibroid (International Federation of Gynecology and Obstetrics types 3–6) accounts for most of the uterine enlargement, but the endometrial cavity is relatively normal in size. **d** | This uterus, viewed at the time of abdominal myomectomy, contained multiple fibroids of ≥10 cm in size. The fallopian tube and ovary can be seen in the middle of the image above the large pedunculated fibroid.



**Figure 2 | Incidence rates of fibroids in different populations.** Age-specific cumulative incidence rates are similar across populations. However, black women have an earlier age of disease onset and higher cumulative incidence of disease (solid red line) than white women (dashed red line). Furthermore, black women (solid blue line) have a higher prevalence than white women (dashed blue line)<sup>196–198</sup>. Adapted with permission from REF. 31, Thieme Medical Publishers, Inc.

### Fibroid stem cells and tissue constituents

The myometrium contains smooth muscle stem cells, known as myometrial stem cells that can transform, under certain conditions, to fibroid progenitors cells<sup>34</sup>. The myometrial stem cells seem to have low-to-absent levels of sex steroid hormone receptors but require these steroids for growth, suggesting that the development of clinical disease is dependent on a paracrine mechanism and a multistep process from transformation to the fibroid progenitor through to growth acceleration. The paracrine mechanism is mediated by the WNT-β-catenin pathway, in addition to oestrogen and progesterone<sup>35</sup>. This pathway can stimulate the expression of transforming growth factor-β3 (TGFβ3), which induces fibronectin (an ECM protein) expression and cell proliferation in preclinical fibroids more than in the myometrium<sup>36</sup>.

As opposed to the traditional view, fibroids seem to consist of at least four components: smooth muscle cells, vascular smooth muscle cells and two types of fibroblasts (fibroblasts and fibroid-associated fibroblasts)<sup>37</sup>. These cell types are clonal, meaning that they are derived from the same cell (that is, the fibroid progenitor cell). The cells exhibit differential expression of fibroid-associated genes: CRABP2 (encoding cellular retinoic acid-binding protein 2), PGR (encoding progesterone receptor B) and TGFBR2 (encoding TGFβ3 receptor 2)<sup>38</sup>. These different gene profiles help to explain the heterogeneity of fibroid biology and clinical type.

In addition, the ECM secreted by fibroblasts is an important component of fibroid pathophysiology. Growth factors that are sequestered in the ECM and might regulate fibroid formation include fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF), proheparin-binding epidermal growth factor-like growth factor (HB-EGF) and platelet-derived growth factor (PDGF)<sup>6</sup>. Moreover, the quantity and topology of the ECM in fibroids is suggested to be altered compared with the myometrium<sup>39</sup>, and some

evidence suggests that solid-state signalling occurs when mechanical stress triggered by the growth of the fibroid is converted to biochemical cell signalling<sup>40</sup>. Fibroblasts secrete most components of the ECM<sup>41,42</sup> and are, accordingly, the key elements in the pathophysiology of fibroid disease.

### Fibroid genetics

Hierarchical gene clustering has revealed at least four key pathogenetic subgroups of fibroids, depending on somatic mutations or chromosomal alterations in key genes; the mediator complex subunit 12 (*MED12*) group, the high mobility group AT-hook 2 (*HMGA2*) group, the fumarate hydratase (*FH*) group and a rare group associated with deletion of collagen type IV α5 (*COL4A5*) and *COL4A6* (REFS 43,44).

*MED12* mutations seem to drive fibroid formation, with mutations detected in 50–84% of fibroids, and are present in racially diverse cohorts<sup>44–46</sup>. *MED12* is a component of the mediator complex, which is the interface between transcription factors and RNA polymerase<sup>47</sup>. Mutations cluster in highly conserved regions in exon 2 or in the border between exon 1 and exon 2; mutations lead to a penetrant phenotype that seems to affect the interaction between *MED12* and cyclin C, which regulates β-catenin transcriptional activity<sup>44,48</sup>. Fibroids with *MED12* mutations have increased levels of WNT4-β-catenin compared with those without these mutations<sup>49</sup>. Oestrogen and the interaction of the WNT4 pathway along with TGFβ might explain the enhanced growth observed in fibroids with *MED12* mutations. *MED12* mutations have also been identified in rare fibroid variants, including atypical, cellular and lipoleiomyomas, as well as leiomyosarcomas and smooth muscle tumours of uncertain malignant potential (STUMP)<sup>50</sup>. By contrast, *MED12* mutations are present at a lower frequency in these variants than in typical fibroids, suggesting different mechanistic regulation of these lesions<sup>44,50,51</sup>.

Complex chromosomal rearrangements (a type of limited chromothripsis in which chromosome shattering and random reassembly occur) were detected by whole-genome sequencing. This type of chromosomal translocation was previously thought to be limited to malignant tumours but is now known to have a role in fibroid pathogenesis<sup>43,44</sup>. Specific karyotypic rearrangements were found in fibroids, leading to the dysregulation of *HMGA2* (a transcription-regulating factor)<sup>52,53</sup>. The dysregulation of *HMGA2* might be associated with fibroid growth by the increased expression of *CDKN2A* (which encodes ARF (p14)). Intact ARF (p14) maintains senescence in fibroids<sup>54</sup>. An interaction between *HMGA2* and let-7 (a microRNA precursor) might also occur, with possible repression of *HMGA2* via let-7 that causes inhibition of cellular proliferation. Fibroids have the potential to be either deficient in let-7, as seen in larger fibroids, or express increased levels of let-7, as seen in smaller fibroids<sup>55</sup>. The amalgamation of various studies led to the hypothesis that alterations in the let-7–*HMGA2*–ARF (p14) pathway might increase the self-renewal capability and reduce senescence of fibroid

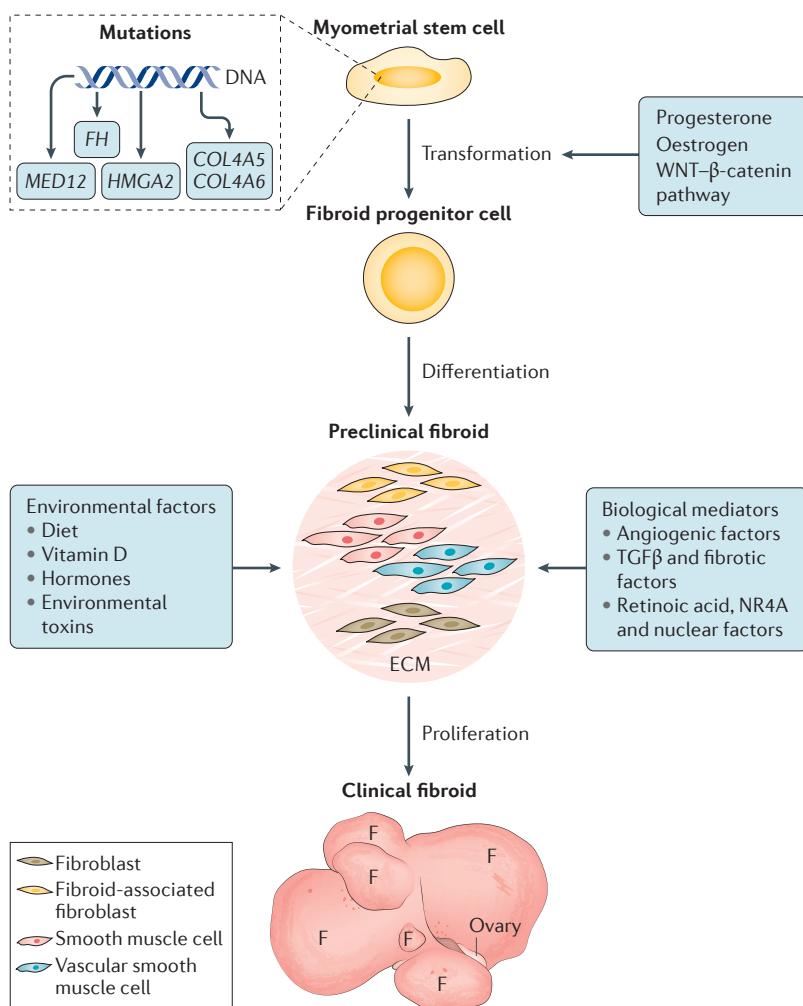
progenitor cells<sup>56</sup>. *MED12* and *HMGA2* mutations seem to be mutually exclusive in fibroids, suggesting distinct pathways<sup>43,49,57</sup>.

The third group is defined by the inactivating mutations of *FH*, a key enzyme involved in the Krebs cycle. Mutations in *FH* are mutually exclusive to *MED12* and *HMGA2* mutations and include missense, frameshift, nonsense and whole-gene deletions, which lead to a fundamental change in cellular metabolism and activates hypoxia signalling<sup>35,58</sup>. Women with *FH* mutations and hereditary leiomyomatosis and renal cell cancer (HLRCC) have a high risk of fibroids, and these women can develop fibroids with a distinct histology (increased cellularity and atypia with multinucleated cells) that are analogous to the lesions that occur in the Eker rat model, which has a germline mutation in tuberous

sclerosis 2 (*TSC2*)<sup>59,60</sup>. There are multiple links between *FH* and *TSC2* mutations, for example, both can be associated with benign skin lesions, hereditary predisposition to cancer and non-malignant lung lesions<sup>61</sup>.

Deletions of the collagen genes *COL4A5* and *COL4A6* are also associated with a familial syndrome, known as diffuse leiomyomatosis with Alport syndrome and rarely with non-syndromic fibroids. Alport syndrome is characterized by diffuse leiomyomatosis of the respiratory, gastrointestinal and genitourinary tracts as well as sensorineural hearing loss<sup>44</sup>. Evidence suggests that there is a synergistic effect between the inactivation of *COL4A5*, *COL4A6* and *IRS4* (encoding insulin receptor substrate 4) underlying the pathogenesis of this syndrome<sup>43</sup>.

Few studies have investigated the epigenetics of uterine fibroids. However, epigenetic changes might be involved in silencing tumour suppressor genes in fibroids. Inactivation of tumour suppressor genes fits with the high frequency of fibroids when the myometrium is examined microscopically<sup>62,63</sup>. Evidence indicates abnormal hypermethylation in a subset of oestrogen receptor (ER) response genes and several tumour suppressor genes, such as *KLF11* (encoding Kruppel-like factor 11), *DLEC1* (encoding deleted in lung and oesophageal cancer protein 1), *DAPK1* (encoding death-associated protein kinase 1) and *KRT19* (encoding keratin type I cytoskeletal 19).



**Figure 3 | Current concepts in the pathogenesis of uterine fibroids.** The pathogenesis of fibroids (F) is a multistep process, starting with the recruitment of a smooth muscle stem cell from the myometrium that lacks receptors for the gonadal steroids. However, under the influence of specific driver mutations, in addition to oestrogen, progesterone and WNT-β-catenin signalling, the stem cell differentiates into a preclinical fibroid. Subsequently, four key cell types that comprise fibroids (smooth muscle cells, vascular smooth muscle cells, fibroblasts and fibroid-associated fibroblasts) and the extracellular matrix (ECM) synergize with environmental and molecular stimuli to undergo growth acceleration and progression into clinical disease. NR4A, nuclear receptor 4A; TGFβ, transforming growth factor-β.

### Nuclear receptors

Oestrogen and progesterone and their receptors (ER and PR, respectively) have long been considered as key regulators of fibroid biology (FIG. 4). Both ERα and ERβ are expressed in fibroids following the differentiation of fibroid progenitor cells<sup>64</sup>. However, oestrogens binding to ERα have more of a permissive function than through the induction of PR by progesterone<sup>34</sup>. Polymorphisms in the receptors and elements of their signalling pathways might also be involved in fibroid biology<sup>65</sup>. Furthermore, there is evidence that increased local aromatase expression has a role in fibroid biology, especially in black women<sup>66</sup>.

Increasing clinical use of PRMs to treat fibroids suggests that progesterone might be a more important regulator of fibroid growth than oestrogen<sup>67,68</sup>. This notion corroborates with *in vitro* evidence from a rodent xeno-graft model that revealed progesterone as the primary regulator of fibroid growth and volume maintenance and that oestrogen is primarily important for the induction of the PR<sup>69</sup>. More than likely, there is a complex interaction between these two sex steroids and the interaction with other factors. However, some evidence suggests that the action of progestins, antiprogestins and PRMs in the uterus might be more complex than in tissue such as breast; >7,000 sites in the genome are bound by antagonistic PR complexes (for example, the mifepristone-PR complex), many of which are distant from the transcription start site<sup>70</sup>. One transcription factor that has been shown to be integral to PR signalling and, therefore, for proliferation of fibroid cells is KLF11 (REF. 71). Progesterone and its analogues also have non-genomic

actions that might have functional significance, including activation of the AKT pathway, which promotes fibroid growth through promotion of cell survival and inhibition of apoptosis<sup>72</sup>.

In addition to the ER-ligand and PR-ligand systems, other nuclear receptors and their ligands have key roles in fibroid pathogenesis. A range of clinical and molecular evidence suggests a relationship between vitamin D deficiency and fibroids. Single-nucleotide polymorphisms in the genes involved in vitamin D metabolism have been linked to fibroids<sup>73</sup>, for example, in *ASIP* (encoding agouti signalling protein)<sup>73</sup> and near *DHCR7* (encoding 7-dehydrocholesterol reductase), and serum concentrations of vitamin D are also inversely proportional to the size of individual fibroids<sup>73</sup>. Multiple studies suggest that vitamin D3 induces apoptosis of fibroid cells, alters TGF $\beta$  activity and might modulate the expression of other elements of this pathway, including matrix metalloproteinase 2 (*MMP2*), *MMP9*, TIMP metalloproteinase inhibitor 2 (*TIMP2*) and vitamin D receptor (*VDR*)<sup>73,74</sup>. MMPs are enzymes involved in the degradation of the ECM that is found in excessive amounts in fibroids; MMPs are also regulated by TIMPs.

Retinoic acid is downregulated in fibroids. Retinoids and their six cognate receptors (RAR $\alpha$ , RAR $\beta$ , RAR $\gamma$ , RXR $\alpha$ , RXR $\beta$  and RXR $\gamma$ ) have been identified as important factors in the pathogenesis of fibroids<sup>58,75,76</sup>. Retinoids have been shown to inhibit proliferation and induce apoptosis in fibroid smooth muscle cells but not in smooth muscle cells in the myometrium. Moreover, retinoic acid probably regulates a large number of genes that have altered expression in fibroids, such as *ADH1*, *ALDH1A1*, *RBP1*, *RBP2* and *RDH*, thereby supporting the hypothesis that alterations in the retinoic acid pathway play an important part in fibroid pathophysiology<sup>75</sup>. In addition, retinoids might be linked to fibroid

heterogeneity given that black women have different expression profiles for *RARA* and *RXRA* compared with white women<sup>77</sup>.

Other nuclear receptors involved in fibroid biology include the androgen receptor and the nuclear receptor 4A (NR4A) subfamily. The androgen receptor might have an effect on fibroid aetiology through the overexpression of aromatase, and women who have high levels of testosterone have higher rates of fibroids<sup>78,79</sup>. Members of the NR4A subfamily of nuclear receptors (generally thought to be constitutively active orphan receptors) have been shown to be underexpressed in fibroids and to have a key role in both ECM deposition and cellular proliferation<sup>80</sup>.

### Other systems

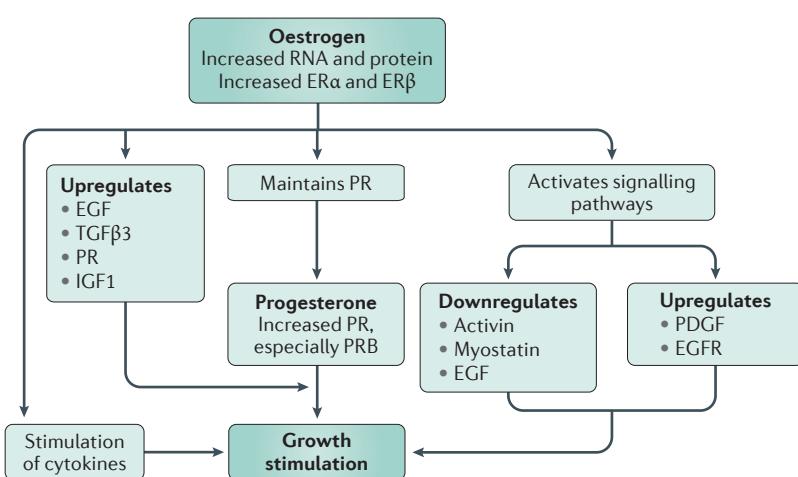
Debate remains as to whether the other myriad genetic alterations identified in uterine fibroids are secondary or causal<sup>81–83</sup>.

Angiogenesis has also been shown to be dysregulated in fibroid-containing uteri. Some studies suggest that fibroids might exhibit an anti-angiogenic gene expression profile compared with the normal myometrium and the myometrium adjacent to fibroids. However, for women with fibroid-associated heavy menstrual bleeding, both the myometrium and the endometrium are also crucial for the development of this symptom<sup>6,82</sup>.

The TGF $\beta$  pathway has been identified as an important regulator of cell growth in fibroids by the modulation of tissue remodelling, inflammation and prevention of apoptosis<sup>84,85</sup>. TGF $\beta$ 3 might also suppress the expression of local anticoagulant factors (such as plasminogen activator inhibitor 1, antithrombin III and thrombomodulin) in adjacent endometrial cells, which contributes to the heavy menstrual bleeding<sup>86</sup>. Similarly, the insulin-like growth factor 1 (IGF1) system could be involved in the preferential promotion of mitosis in fibroid cells over normal myometrial cells<sup>87</sup>.

Some membrane receptor systems have also been implicated in fibroid pathogenesis. For example, the prolactin-releasing peptide receptor (encoded by *PRLHR*), located upstream of the mechanistic target of rapamycin (mTOR) pathway, seems to be abnormally expressed in fibroids, and the loss of the repressor RE1-silencing transcription factor (encoded by *REST*) might play a part in pathogenesis<sup>88</sup>. Prolactin has been shown to be a smooth muscle mitogen in fibroids, is upregulated in fibroids and the prolactin receptor has also been identified in fibroid, myometrial and endometrial tissue<sup>89</sup>.

Other genes altered in fibroids include *CTNNB1* and *NR2F2*. *CTNNB1* is upregulated in fibroids and is important for cell–cell adhesion and the WNT signalling pathway. Upregulation of *CTNNB1* in a mouse model resulted in lesions with similar characteristics to fibroids<sup>81</sup>. Conversely, *NR2F2* is downregulated in fibroids and results in abnormal uterine morphology in a conditional knockout model<sup>81</sup>. Both *CTNNB1* and *NR2F2* share common regulators, including retinoic acid, progesterone and the Sonic Hedgehog systems<sup>81</sup>.

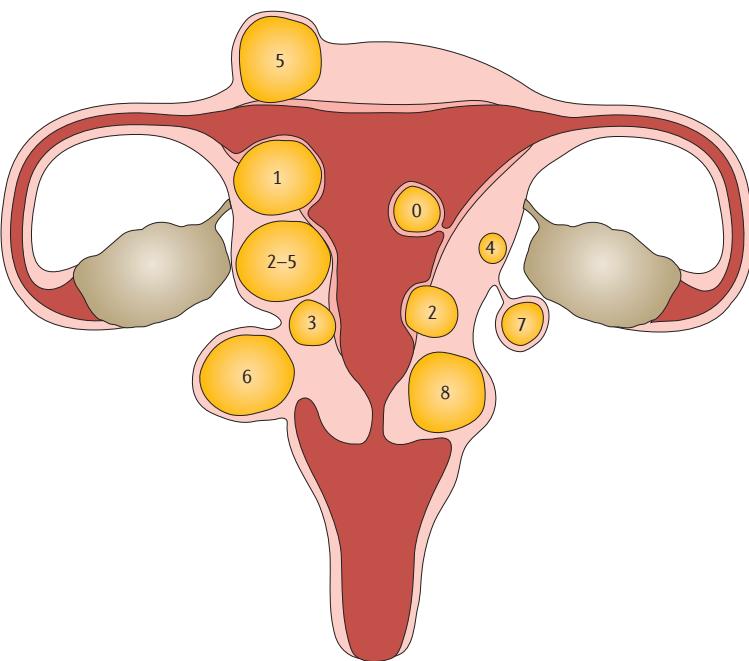


**Figure 4 | The role of sex steroids in uterine fibroids.** Both oestrogen and progesterone play complex and interacting parts in the pathophysiology of uterine fibroids through various mechanisms, including upregulation of growth factors, activation of signalling pathways and maintenance of the progesterone receptor (PR). EGF, epidermal growth factor; EGFR, EGF receptor; ER, oestrogen receptor; IGF1, insulin-like growth factor 1; PDGF, platelet-derived growth factor; PRB, PR type B; TGF $\beta$ 3, transforming growth factor- $\beta$ 3.

### Box 1 | Fibroid subclassification system\*

Fibroids are heterogeneous in their size and location. A staging system has been developed by the International Federation of Gynecology and Obstetrics (FIGO) that indicates the location of fibroids relative to the mucosal and serosal surfaces (see the figure)<sup>95</sup>. However, this classification does not indicate the size of fibroids and underestimates the complexity of the clinical disease.

- Type 0: pedunculated fibroid, which is localized in the submucosa and extends inside the uterine cavity
- Type 1: submucosal fibroid, with <50% in an intramural location
- Type 2: submucosal fibroid, with ≥50% in an intramural location
- Type 3: contacts the endometrium, with 100% in an intramural location
- Type 4: intramural fibroid
- Type 5: subserosal fibroid, with ≥50% in an intramural location
- Type 6: subserosal fibroid, with <50% in an intramural location
- Type 7: subserosal pedunculated fibroid
- Type 8: other (for example, cervical or parasitic)



\*This classification includes hybrid classifications, for example, FIGO types 2–5 for transmural fibroids. Adapted from the Korean Medical Association.

### Animal models

For many years, the Eker rat strain and the cell lines generated from this model were widely used in fibroid research<sup>90,91</sup>. This model was created with a germline retrotransposon insertion in *TSC2*, resulting in a model system for HLRCC<sup>90,91</sup>. Although not associated with uterine leiomyomas, lymphangioleiomyomatosis, another proliferative disease involving smooth muscle cells, is caused by the dysregulation of *TSC2* (REF. 1). Because of this, the Eker rat model is commonly used as a model of lymphangioleiomyomatosis in addition to uterine fibroids. However, several limitations are associated with the Eker rat model, including the cost of housing animals, the lack of a rat genome map and that lesions in these animals had some phenotypic characteristics that were more suggestive of malignancies than benign fibroids. In the past few years, progress has been

made in developing murine models using subcutaneous and subrenal capsule xenografts of human tissue in immunocompromised mice<sup>92,93</sup>. However, other murine models<sup>88</sup> and cost-effective models using the domestic hen are also being examined<sup>94</sup>.

### Diagnosis, screening and prevention

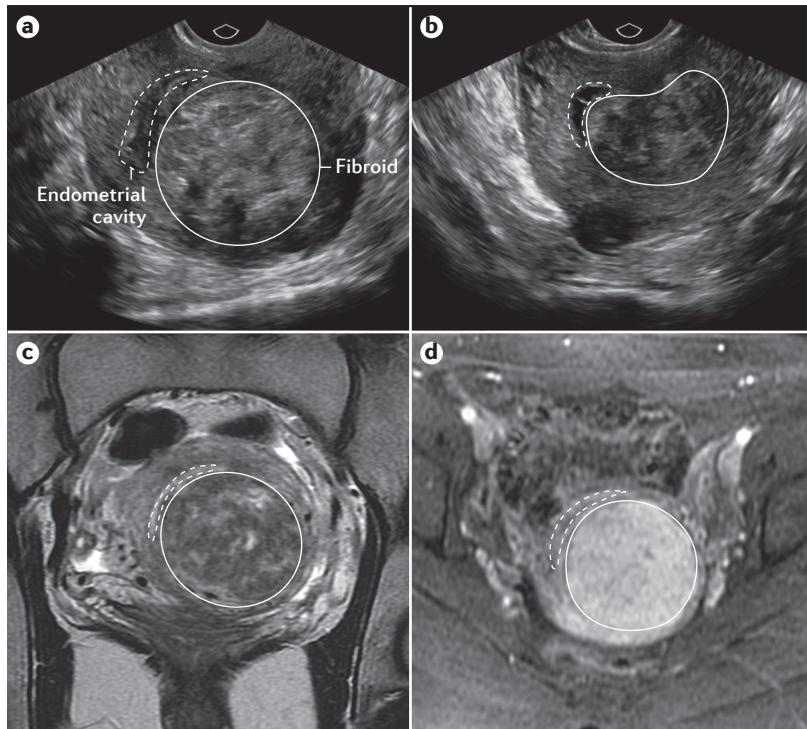
#### Diagnosis

The diagnosis of uterine fibroids is complicated by numerous factors: diversity in the size, location and number of fibroids between patients and fibroid symptoms can be variable. Moreover, the symptoms of fibroids are relatively common and can be associated with other factors or diseases, such as ovulatory dysfunction, endometriosis or endometrial polyps. Many women do not connect their symptoms to fibroids, so can go undiagnosed for some time, and some fibroids can be asymptomatic, thereby avoiding detection.

The International Federation of Gynecology and Obstetrics (FIGO) has established a classification system of the causes of abnormal uterine bleeding in women of reproductive age, based on data obtained from imaging. The system uses an 8-point numerical system to describe the location of fibroids relative to the endometrium (submucosal surface) and the serosal surface, with low numbers indicating a central location<sup>95</sup> (BOX 1). This classification should result in an improved description of uterine fibroids during clinical trials and should help to determine which fibroids are likely to be associated with heavy menstrual flow. Furthermore, the transition of the terminology from Latin-derived and Greek-derived terms, such as menorrhagia, to clearer definitions, for example, ‘heavy menstrual bleeding’, should enable improved communication<sup>95</sup>. Improved precision in these terms will result in greater confidence in the benefits of various therapeutic interventions.

Symptoms of fibroids can include gynaecological, urinary and gastrointestinal problems. Heavy menstrual bleeding is the most common symptomatic complaint from women with fibroids, but other gynaecological symptoms include prolonged menstrual bleeding, pelvic pressure and pain, as well as bleeding between menstrual periods. Excessive bleeding can lead to the development of anaemia. Urinary symptoms of fibroids include increased urinary frequency, incontinence and hesitancy. Although rare, fibroids can also cause obstruction of the ureter, which might require treatment if this progresses to severe hydronephrosis. Gastrointestinal symptoms such as constipation and tenesmus (the recurrent need to void bowels) can also be caused by fibroids. Backache and leg pain can also be observed in some patients<sup>96</sup>.

During pregnancy, women with fibroids have an increased risk of complications compared with women without fibroids, including preterm delivery (16.7% versus 6.3%) and premature rupture of membranes (14.3% versus 2.1%). Moreover, the risk of placental abruption (7.5% versus 0.9%), fetal malformation (6.2% versus 3.3%), caesarean section (70–76% versus 32.8%), postpartum haemorrhage (33% versus 6%) and fetal malpresentation (19% versus 4.4%) are increased



**Figure 5 | Imaging modalities for uterine fibroids.** **a** | Transvaginal ultrasonography is the most commonly used imaging modality for the detection of fibroids. A heterogeneous fibroid between 8 cm and 9 cm in size (solid white border) is seen near the endometrium (dashed white border). **b** | An intracavitary fibroid (probably International Federation of Gynecology and Obstetrics type 2; solid white border) can be observed following sonohysterography. **c** | A T2-weighted MRI scan showing a fibroid (solid white border) on the right and the endometrial cavity (dashed white border) on the left and superior to the fibroid. **d** | The good blood supply of this fibroid (solid white border) can be visualized in an axial view with intravenous gadolinium-enhanced MRI.

in women with fibroids<sup>97–100</sup>. Fibroids might also be associated with miscarriage.

The location of fibroids directly affects the symptoms they induce, as well as the time to the manifestation of such symptoms. For example, submucosal fibroids seem to have more of an effect on abnormal menstrual bleeding and pregnancy problems. This is independent of fibroid size as small fibroids that protrude into the uterine cavity can also induce menstrual irregularities<sup>101</sup>. Conversely, subserosal fibroids are slow growing and considerable time is needed before they are of a sufficient bulk to cause symptoms, such as back, leg or pelvic pressure and abdominal and pelvic pain.

**Imaging.** During clinical examination, the identification of a firm, multilobular uterus or palpable firm masses extending from the uterus strongly suggests the presence of uterine fibroids. However, in clinical practice, ultrasonography is used to examine and conclusively identify fibroids and exclude other conditions such as ovarian cancer. The percentage of women diagnosed with uterine fibroids is 17% using bimanual palpation, but increases to 25.8% with the use of transvaginal ultrasonography<sup>102</sup>.

Among patients who presented in one study with heavy menstrual bleeding (approximately 25% of all cases), the probability of diagnosing uterine fibroids by

transvaginal ultrasonography was 73.3%<sup>103</sup>. The sensitivity and specificity for transvaginal ultrasonography were 90% and 87%, respectively, both of which were improved with the addition of sonohysterography (that is, instilling saline into the uterine cavity) up to 100% and 98%, respectively<sup>104,105</sup>.

Other imaging modalities can be used to effectively diagnose fibroids. For example, hysterosalpingography (that is, X-ray examination of the uterus and fallopian tubes) can also be used to diagnose uterine fibroids. However, the sensitivity and specificity of this test (50% and 20%, respectively) are inferior to transvaginal ultrasonography, owing to the lack of real-time 3D continuous images<sup>104,105</sup>. MRI can also be used in fibroid diagnosis<sup>106</sup>. Although substantially more expensive and labour intensive than ultrasonography, the sensitivity and specificity of MRI is close to 100%. MRI is generally required for accurate diagnosis in a minority of patients, such as women with a larger body habitus, who have had prior surgery, or do not tolerate either the transvaginal probe or the transvaginal installation of contrast media. Moreover, the additional information gained by MRI might be useful for planning complex surgery or procedures that require visualization of fibroid vascularization, such as uterine artery embolization (UAE) and magnetic resonance-guided focused ultrasound (MRgFUS) treatment (see below)<sup>107</sup>. As the prevalence of uterine fibroids increases with age, the predictive value of these tests also increases.

Transvaginal ultrasonography remains the primary imaging modality for the diagnosis of uterine fibroids owing to the benefits of lower cost associated with this test, in addition to the reliable identification of calcified fibroids and the detection of larger, clinically relevant fibroids (FIG. 5a). However, differentiating small submucosal fibroids from the surrounding endometrium is difficult by standard transvaginal ultrasonography, even though they can induce heavy bleeding. This limitation can be overcome by sonohysterography coupled with ultrasonography (FIG. 5b), thereby isolating the submucosal fibroid with surrounding non-echogenic fluid. In patients presenting with abnormal uterine bleeding, the sensitivity and specificity of saline sonography (89.5% and 100%, respectively) are superior to standard transvaginal ultrasonography (70% and 96.6%, respectively)<sup>108</sup> for the diagnosis of submucosal fibroids.

The use of standard transvaginal ultrasonography is also limited when the uterus extends beyond the pelvis, a common problem with this disease. Abdominal ultrasonography might be required to diagnose fibroids that extend beyond the effective range of the transvaginal probe, but MRI is generally preferred for this purpose. Although the volume of the single largest fibroid can be accurately determined by either technique, ultrasonography typically underestimates fibroid volume when compared with MRI. Moreover, the total number of detected fibroids differs when imaged using ultrasonography or MRI in >70% of patients<sup>109</sup>. In clinical scenarios in which imaging is required for surgical planning, or if the size of the fibroid must be accurately estimated, MRI might be superior (FIG. 5c,d).

Imaging is also an effective means of screening for patients who present with infertility only, who might have fibroids that could be disrupting the ability of achieving or sustaining pregnancy. In these women, transvaginal ultrasonography is effective at identifying fibroids located within the myometrium but cannot assess the potential tubal obstruction caused by the compressive effect of subserosal fibroids. Fibroids that affect the endometrial lining (FIGO types 0–3) can be assessed using saline sonography in conjunction with transvaginal ultrasonography, and intrauterine defects and tubal patency can be assessed by hysterosalpingography MRI. MRI can be used for preoperative mapping of fibroids in these women.

**Histological evaluation.** The classic histological presentation of fibroids involves spindle-shaped smooth muscle cells arranged in disoriented fascicles, separated by substantial ECM. Moreover, fibroids that are present with well-circumscribed borders, bland cytology and little mitotic activity (mitotic index of  $\leq 2$  per 10 high power fields). The nuclei of cells that comprise fibroids are defined by focal nuclear membrane irregularities without atypia and small conspicuous nucleoli<sup>110</sup>.

Histological assessment of the malignant potential of fibroids is made by the evaluation of nuclear grade or atypia, in addition to the number of mitoses and the presence or absence of coagulative necrosis. Over 10 mitoses in 10 high power fields are strongly suggestive of leiomyosarcoma, particularly when associated with moderate atypia or coagulative necrosis. However, <10 mitoses per 10 high power field does not always guarantee the diagnosis of fibroids. The presence of gross degeneration alone is insufficient for the diagnosis of leiomyosarcoma, as such histological changes might also be observed in STUMP lesions<sup>110</sup>. Conversely, the absence of degeneration does not guarantee a benign clinical diagnosis, although the likelihood of malignancy is rare in this scenario.

Histological examination has revealed that benign fibroid variants can demonstrate a range of pathological abnormalities, commonly including hyaline degeneration, cellular or atypical (symplastic) leiomyomas<sup>111</sup>.

**Biomarkers.** To date, identified serum-based biomarkers lack adequate predictive value to improve on physical examination and imaging for diagnosis. Several biomarkers have been examined, including prolactin, soluble human leukocyte antigen (HLA) class I histocompatibility antigen- $\alpha$  chain G (also known as HLA-G antigen), VEGF, appetite-regulating hormone (also known as ghrelin), lactate dehydrogenase and mucin 16 (also known as cancer antigen 125 (CA125))<sup>112</sup>. Among women with leiomyomas, biomarkers could be clinically useful if they were able to accurately identify women at higher risk of developing rapidly growing fibroids compared to those with relatively static disease.

Biomarkers would also be useful to distinguish benign uterine fibroids from other conditions. For example, adenomyosis has numerous similarities to uterine fibroids as both conditions present as hyperplastic processes in the myometrium and can be associated with heavy menstrual bleeding<sup>113</sup>. In addition, adenomyosis has parallels

to endometriosis as both disorders are manifestations of ectopic endometrial glands and stroma, as well as being associated with pelvic pain. Interestingly, adenomyosis also has unique structural and functional characteristics arising from the involvement of the junctional zone of the myometrium<sup>114</sup>. Both MRI and ultrasonography can in some cases differentiate between fibroids and adenomyosis, but the only definitive way to do this is by the histological examination of surgically excised tissue<sup>114</sup>. Diagnostic criteria for adenomyosis have been developed based on the use of these imaging modalities<sup>115</sup>.

### Screening

**Self-reporting.** Self-reporting is a patient presenting with the suspected diagnosis of uterine leiomyomas, based on the experiencing of symptoms associated with this disorder.

Overall, black women had a higher sensitivity of self-report than white women, which increased with age from 12% in black women between 18 and 29 years of age to 41% in those 35–45 years of age<sup>26</sup>. This finding could be explained by the enhanced severity of disease burden in black women or a greater awareness of the known racial disparities in fibroid development. Finally, the ability to report the absence of fibroids (specificity) was extremely high and almost equal between black women (98%) and white women (97%), respectively<sup>15</sup>.

Other factors, aside from ethnicity, that can affect the self-reporting of fibroids, include childbirth history, level of education and the size of the fibroid. Women with a history of childbirth have a higher sensitivity of self-report, which could be related, for example, to a greater self-awareness of pelvic pressure following childbirth, or owing to greater experience of self-reporting with age. Interestingly, black women with tertiary education had a higher sensitivity of self-report than those with less education. The size of fibroids has also been shown to affect self-reporting. After adjusting for age and parity, sensitivity was three to four times as high in women with fibroids >4 cm in diameter compared with patients whose largest tumour was <2 cm in diameter. This finding can be explained by the presence of increased symptoms with larger tumours.

**Clinical evaluation.** Currently, there are no routine screening programmes available for uterine fibroids, including for women who are considered at being high risk of developing fibroids. However, among women presenting with infertility only, in the absence of other fibroid-associated symptoms, imaging is an effective means of screening for patients who might have fibroids that could be disrupting the ability of achieving or sustaining pregnancy.

**Related lesions.** The symptomatology, imaging and biomarkers, for example, CA125, between fibroids and leiomyosarcomas overlap substantially<sup>116–118</sup>. Accordingly, controversy exists regarding the optimal method of providing minimally invasive therapy for women with symptomatic fibroids because of the current inability to distinguish between these entities preoperatively<sup>119</sup>.

Screening for risk factors, such as increasing age, postmenopausal status, tamoxifen use and HLRCC, as well as taking into account abnormal imaging and biomarker results, can help to identify women with suspected fibroids who have a higher risk of sarcomas. However, given the rapid growth in fibroids observed in premenopausal women, assessing growth is only helpful in the screening of postmenopausal women<sup>5</sup>. Appropriate counselling for all patients must take into account the benefit of minimally invasive surgery for the treatment of fibroids.

### **Prevention**

Given the very high lifetime prevalence of uterine fibroids, it is plausible that, with long enough exposure to cyclic menses, all women would probably develop leiomyomas. Thus, the primary aim of prevention efforts would be to limit the number and size of fibroids, therefore minimizing symptoms and optimizing pregnancy for women who desire to have children. The risk factors with the greatest effect on fibroid development, for example, age, ethnicity and family history, are not modifiable, but reproductive factors and diet can be altered, which might aid prevention of fibroids<sup>120</sup>.

**Potential nutritional supplements.** All current therapeutics aim to provide relief from the symptoms associated with fibroids. Although no interventions are currently available for primary prevention, exciting potential therapies are emerging for secondary prevention. For women who have identifiable leiomyomas but who are currently asymptomatic, a therapy that inhibits or delays fibroid growth could enable a patient to achieve their symptomatic and reproductive goals without the need for surgical or radiological intervention. However, such a therapy must have minimal (or no) adverse effects and convenient dosing. Currently, the interventions with the best potential are supplements that could be added to a patient's diet.

Nutritional supplements with some evidence of therapeutic efficacy in the secondary prevention of uterine fibroids include vitamin A<sup>121</sup>, vitamin D<sup>122</sup>, curcumin<sup>123</sup>, resveratrol<sup>124</sup>, isoliquiritigenin<sup>125</sup>, epigallocatechin gallate<sup>126</sup> and *Euonymus alatus*<sup>127</sup>. Additional data is needed to support the use of nutritional supplements to prevent fibroids or fibroid recurrence.

### **Management**

Appropriate guidelines for the treatment of uterine fibroids are suboptimal, owing to a paucity of high-quality evidence from randomized controlled trials<sup>128</sup>. Moreover, few large prospective cohorts have been recruited to enable the testing of specific therapies and to control for confounding factors, including age and ethnicity, in addition to the size, location and number of fibroids. Thus, many learned society recommendations are not based on strong clinical evidence<sup>129–131</sup>. Current treatment options for symptomatic fibroids include medical, radiological and surgical interventions.

For patients with asymptomatic fibroids, most, but not all, evidence-based guidelines support no therapeutic intervention, but recommend follow-up evaluations<sup>129–131</sup>.

Currently, no accepted standard for the interval between evaluations is available, although some guidelines suggest an annual review<sup>131</sup>. Some fibroids have been shown to regress and this appears more commonly after menopause or childbirth<sup>5,132,133</sup>. There is also some data indicating that decelerated fibroid growth when women approach menopause occurs in white women only, as black women have higher fibroid burden. Accordingly, expectant perimenopausal management of fibroids is typically less successful in black women than in white women<sup>5</sup>.

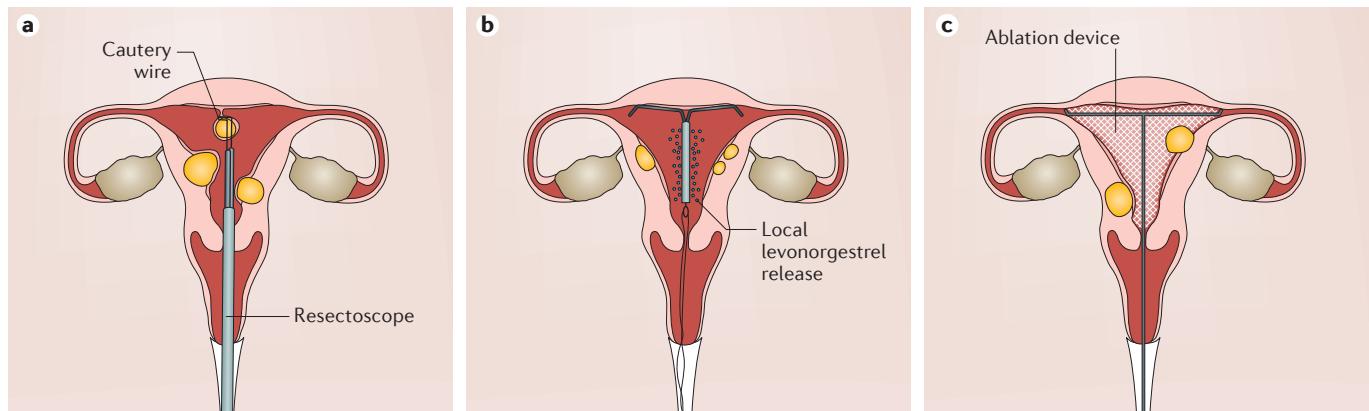
Few data exist to determine which symptomatic fibroids can be managed expectantly and for how long. For premenopausal women with symptomatic fibroids, other commonly associated comorbidities, such as ovulatory disorders, adenomyosis, endometriosis, endometrial polyps and endometrial hyperplasia, warrant consideration as alternative causes of symptoms before ascribing them to the fibroid disease process, and the nature of the symptoms of fibroids dictates the course of treatment<sup>120</sup>. For example, women who have isolated heavy menstrual bleeding have different treatment options to women with either isolated bulk symptoms or bulk symptoms and heavy bleeding (FIGS 6,7).

### **Fibroid-related heavy menstrual bleeding**

**Hysteroscopic myomectomy.** For women with a FIGO type 0 or type 1 fibroid ( $\geq 50\%$  of the fibroid is situated within the uterine cavity; BOX 1), the preferred therapeutic option for the treatment of fibroid-associated menstrual bleeding is hysteroscopic myomectomy (FIG. 6a). Hysteroscopic myomectomy is a same-day surgery with no incisions and a recovery time of just a few days. Importantly, some guidelines also advocate the use of this procedure in asymptomatic women who want future childbearing, given its minimal morbidity and the likelihood of the development of symptoms in the absence of treatment<sup>130</sup>. When performed by expert surgeons, heavy menstrual bleeding associated with some FIGO type 2 fibroids can also be treated by hysteroscopic myomectomy. However, this carries a higher risk of the need for a second hysteroscopic myomectomy<sup>130,134</sup>. For women with fibroids classified as FIGO types 3–8 who do not wish to become pregnant, medical management is the first step in the treatment of fibroid-associated heavy menstrual bleeding.

**Medical treatment.** A range of medical therapies are available for the treatment of symptomatic fibroids, including NSAIDs, antifibrinolytics and contraceptive steroids including the levonorgestrel intrauterine device. However, a systematic review reported the lack of high-quality evidence supporting the effectiveness of most medical therapies for symptomatic fibroids<sup>128</sup>. However, the absence of high-quality evidence does not necessarily suggest the possibility of harm or the lack of therapeutic benefit with these treatments.

NSAIDs have been shown to decrease the painful menses and heavy menstrual bleeding associated with fibroids compared with placebo treatment, but to a lesser extent than with the use of hormonal medications<sup>135</sup>.



**Figure 6 | Treatment options for fibroid-associated heavy menstrual bleeding.** There are a range of treatment options available for women with fibroid-associated heavy menstrual bleeding. **a** For most women with International Federation of Gynecology and Obstetrics (FIGO) type 0 and type 1 fibroids, hysteroscopic myomectomy is the preferred treatment. This outpatient procedure involves transvaginal insertion of the resectoscope to remove the fibroid. **b** For most other women, medical therapies (such as NSAIDs and oral contraceptives) are generally the first-line treatments because of their low cost and added benefit of concurrent contraception. A levonorgestrel intrauterine device can also be used as it provides reversible contraceptive benefit. **c** For women who do not want future pregnancies and have FIGO type 3 or higher fibroids, endometrial ablation might be used to destroy the endometrium. However, contraception is required after this treatment to prevent ectopic pregnancies.

However, NSAIDs are inexpensive and are available without a prescription in most countries. Heavy menstrual bleeding associated with uterine fibroids is at least partly due to local fibrinolysis, therefore, antifibrinolytics are also useful agents. The antifibrinolytic drug tranexamic acid is often used as a first-line therapy, as it was shown to cause a significant reduction in menstrual blood loss when compared with a placebo group. Moreover, tranexamic acid is well tolerated and has a favourable safety profile<sup>136,137</sup>. Both NSAIDs and antifibrinolytics reduce fibroid-associated heavy menstrual bleeding, although they do not alter the size of fibroids.

Contraceptives containing synthetic analogues of oestrogen and progesterone are the most widely used medical therapy for the treatment of fibroid-associated heavy menstrual bleeding. This is not surprising given that oestrogen and progesterone are key regulators of fibroid pathophysiology and also that fibroids are primarily found in women who are of childbearing age. Limited data from randomized controlled trials indicate that the progestin-containing levonorgestrel intrauterine device is effective in decreasing the heavy menstrual bleeding observed in women with fibroids in which the fibroids do not distort the endometrial cavity<sup>138,139</sup> (FIG. 6b). This device also provides long-acting reversible contraception by inducing endometrial atrophy. Levonorgestrel has been shown to inhibit the proliferation and induction of apoptosis in fibroid cells in cell culture studies, but no clinical reduction in fibroid size has been observed following treatment with a levonorgestrel intrauterine device<sup>140,141</sup>. Unfortunately, there is an increased risk of expulsion of the levonorgestrel intrauterine device in women with fibroids (12–16% over up to 3 years). However, currently no data are available about the fibroid or uterine configuration that makes this expulsion more likely<sup>142,143</sup>. Concerns have also been raised

about the long-term cardiovascular effects of systemic levonorgestrel, but confirmatory studies are needed<sup>144</sup>. Other long-acting reversible contraceptives that contain progestins only, such as depot medroxyprogesterone acetate, or contraceptive implants have been shown to be associated with a decreased risk of fibroids in small studies<sup>24</sup>. However, the efficacy of progestin-only treatments in promoting symptomatic relief following fibroid development has not yet been studied. The use of non-contraceptive doses of oral progestins is not beneficial in treating fibroid-associated heavy menstrual bleeding<sup>138</sup>.

Data from observational studies indicate that the use of combined oral contraceptives (containing both oestrogen and progesterone analogues) can also help to control the abnormal uterine bleeding that is associated with fibroids<sup>130,145</sup>. However, uterine fibroids should not be considered a contraindication for the use of combined oral contraceptives, as was previously taught, for fear of prompting fibroid growth.

**Surgical therapy.** Surgical therapy is generally a second-line option for women with FIGO type 3 and higher fibroids and isolated heavy menstrual bleeding, and is used following the failure of medical therapy. Endometrial ablation is a minimally invasive surgical technique used for the destruction of the endometrial lining and can be used in women who do not want future pregnancies. It can be used either in combination with hysteroscopic myomectomy or alone in women with or without submucosal fibroids, respectively (FIG. 6c). However, endometrial ablation is less preferable than a levonorgestrel intrauterine device, given that the procedure cannot be reversed and does not provide contraception; women are at risk for extrauterine pregnancies following endometrial ablation. Hysterectomy with ovarian conservation is another effective option

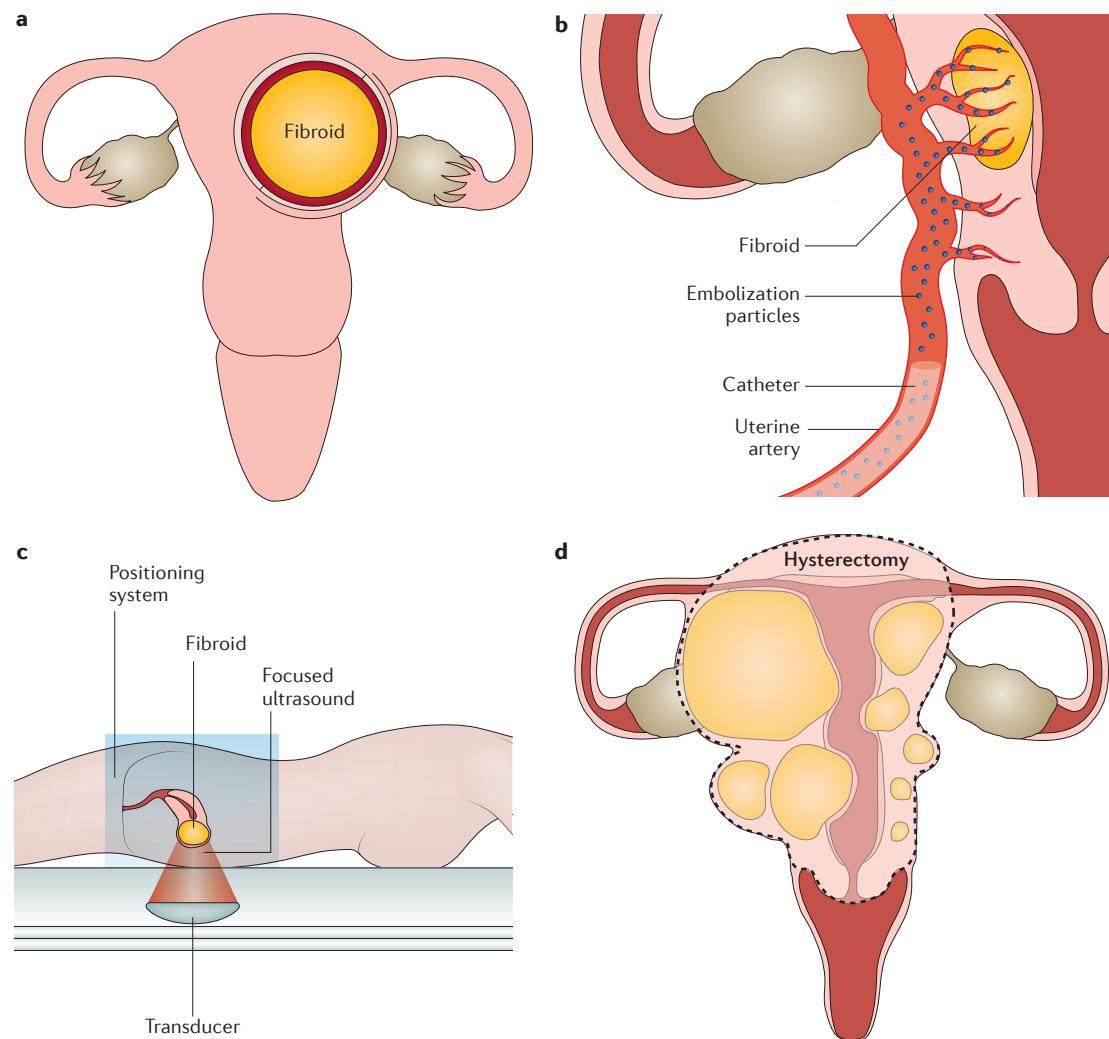
for women with fibroid-associated heavy menstrual bleeding who are not pursuing pregnancy. However, this procedure entails substantially more morbidity than the less-invasive options, such as endometrial ablation.

For women with severe fibroid-associated heavy menstrual bleeding who are trying to optimize pregnancy, intramural fibroids can be removed with laparoscopic, robotic or abdominal myomectomy. Minimally invasive surgical procedures (laparoscopic and robotic) are generally preferred to abdominal myomectomy, which is generally reserved for large fibroids (>10 cm in diameter) (FIG. 7). However, a complete fertility evaluation assessing ovulation, ovarian reserve, tubal patency, in addition to the semen of the male partner should be undertaken before this step to delineate the cause of

infertility. Other disorders that could cause infertility need to be treated earlier than the surgical treatment of fibroids, which might negatively affect the fertility of the patient, subsequent to adhesion formation or other damage to pelvic structures.

#### Bulk fibroid symptoms

For women with symptoms related to the size of the fibroid, either in isolation or in combination with heavy menstrual bleeding, treatments associated with a change in the size or composition of the fibroids are necessary. Both medical and surgical options are available for the treatment of these fibroids, and the manipulation of gonadal steroids again predominates within medical options.



**Figure 7 | Surgical options for fibroid-associated bulk symptoms with or without heavy menstrual bleeding.** Various treatment options are available for women with symptoms depending on the size of the fibroids. For those women who wish to optimize pregnancy, myomectomy is often the first line of treatment (part a). Here, the fibroid is excised, and the uterus is left intact and its volume reduced. The procedure can be performed open (with abdominal incision), laparoscopically or robotically assisted. Alongside uterine artery embolization (part b), in which the blood supply to the fibroid is obstructed, other uterine-sparing options include surgical radiofrequency ablation and magnetic resonance-guided focused ultrasonography (part c). In the latter, focused ultrasound energy targets the fibroid. These two techniques (uterine artery embolization and focused ultrasonography) shrink and soften the fibroid to reduce morbidity. Hysterectomy remains an option for women who have failed primary therapies or have other concomitant diseases (part d).

**Selective PRMs.** PRMs are rapidly becoming the standard medical option for fibroids associated primarily with bulk symptoms and are used preoperatively and as a short-term medical therapy in most of the world. PRMs have a rapid onset of action and are effective at reducing both fibroid and uterine volume, in addition to heavy menstrual bleeding, anaemia and pain<sup>68,120,146</sup>. Although several PRMs have been investigated in clinical trials, ulipristal acetate (UPA) has received CE marking for both preoperative and intermittent repeated courses of therapy in the European Union and is also undergoing further evaluation in other countries. Randomized controlled trials have confirmed the efficacy and safety of UPA therapy continuously for 3 months compared with placebo or GnRH agonists<sup>67,68</sup>. Because of both the anti-neoplastic action of progesterone on the endometrium and the unusual pathological PRM-associated endometrial changes, which currently are not believed to be precancerous, intermittent treatment with PRMs (interrupted by menstruation) has been adopted<sup>131,147,148</sup>. So far, the longest examined duration is <2 years, intermittent therapy for four cycles each of 3 months in duration and with menstruation in drug-free intervals<sup>68</sup>. Studies testing the safety and efficacy for longer duration of treatment are in progress.

A sustained long-term effect of 3–12 months of UPA therapy on fibroid volume reduction and menstrual bleedings has been suggested in data obtained from a retrospective case series of 18 successful pregnancies occurring for up to 6 years following completion of UPA therapy<sup>149</sup>. Longer duration of treatment has not yet been evaluated. Unfortunately, appropriate doses of UPA for the treatment of fibroids are currently not available in the United States. However, some fibroids have been shown to be resistant to UPA treatment and, currently, there is no way to determine which fibroids will respond to UPA therapy.

In addition to UPA, other PRMs, especially mifepristone, have been widely studied for the treatment of bulk fibroid symptoms. These other PRMs have shown similar benefits but have not yet been approved as clinical therapies<sup>150</sup>. In one study<sup>151</sup>, glutathione S-transferase Mu 1 (GSTM1), an enzyme involved in the metabolism of steroids, reactive oxygen species, xenobiotics and drugs, and thus the regulation of vascular smooth muscle cells, was found to be a marker for the reduction in fibroid volume associated with mifepristone treatment. Mifepristone is not approved by the US FDA for the treatment of uterine fibroids at this time.

**GnRH agonists.** GnRH agonists are effective medical therapies for uterine fibroids and are generally used preoperatively for a duration of 3–6 months in combination with iron therapy to facilitate endoscopic or transvaginal surgery<sup>152,153</sup>. In contrast with PRMs, GnRH agonists have a slower onset of action as they first stimulate the pituitary gland and ovaries in a phenomenon known as the flare effect, then lead to downregulation of GnRH receptors and cause substantial hypoestrogenic symptoms<sup>154,155</sup>. After the initial downregulation, add-back therapy with low-dose oestrogen and progestin

can be considered to minimize the menopausal symptoms observed when long-term GnRH agonist therapy is required. Results from a meta-analysis suggest that treatment with GnRH agonists might improve some fibroid outcomes in terms of symptom relief from bulk symptoms, heavy menstrual bleeding and dysmenorrhoea when used before hysteroscopic myomectomy, but insufficient evidence substantiates their routine use<sup>156</sup>.

**GnRH antagonists.** GnRH antagonists have similar benefits to GnRH agonists with the added advantage of the rapid onset of clinical effects without the flare effect. Mechanistically, GnRH antagonists compete with GnRH for receptors on gonadotropic cell membranes, inhibit GnRH-induced signal transduction and, consequently, inhibit the secretion of GnRH. Thus, the initial flare effect seen with GnRH agonists does not occur with these drugs<sup>157</sup>. Currently, however, GnRH antagonists are only licensed for ovulation induction protocols and long-acting preparations are not available.

**Other medical agents.** Although preclinical data has indicated the strong efficacy of selective ER modulators in the treatment of uterine fibroids, they have produced disappointing results in clinical trials<sup>158,159</sup>. Likewise, aromatase inhibitors have also been investigated for the treatment of bulk fibroid symptoms, including trials carried out exclusively in perimenopausal women. However, current data does not support their use as a medical therapy<sup>160,161</sup>. These data support the increasing evidence that suggests the importance of progesterone in fibroid pathogenesis. Androgenic steroids have also been studied for the treatment of fibroids, but there is limited data showing their effectiveness<sup>162</sup>.

**Interventional and surgical therapies.** The paradigm is changing for women with fibroids and bulk symptoms, owing to the increasing use of minimally invasive treatments beyond conventional surgical excision of fibroids, such as myomectomy and hysterectomy.

Myomectomy removes fibroids and preserves the uterus, but owing to the development of less-invasive alternatives to hysterectomy, such as UAE, myomectomy is primarily used for women who are actively seeking pregnancy<sup>129</sup> (FIG. 7a). Laparoscopic and robotic myomectomy with resection of fibroids with removal by morcellation (that is, shredding the tumour for removal) was growing in use until the FDA issued warnings about the potential for morcellation to disseminate cancer in cases with unsuspected uterine sarcomas<sup>119</sup>. Current guidelines recommend restricting the use of morcellation to the treatment of fibroids in premenopausal women when en bloc resection is not feasible and counselling about the risks of sarcoma dissemination has taken place<sup>119</sup>.

Compared with laparoscopic myomectomy, laparoscopic radiofrequency ablation with intra-abdominal ultrasound guidance results in less blood loss and shorter hospital stays and is another approved procedure for the treatment of fibroids associated with bulk symptoms<sup>163,164</sup>. Several other laparoscopically directed

**Box 2 | Validated instruments for specific symptoms**

- Uterine Fibroid Symptom and Quality Of Life<sup>178</sup>
- Aberdeen Menorrhagia Clinical Outcomes Questionnaire for heavy menstrual bleeding<sup>190</sup>
- Menstrual Pictogram for heavy menstrual bleeding<sup>191</sup>
- Menstrual Distress Questionnaire<sup>192</sup>
- Female Sexual Function Index<sup>193</sup>
- Visual Analogue Scale<sup>194</sup> and McGill Pain Score<sup>195</sup>

techniques have also been reported for the treatment of fibroid-associated bulk symptoms, including cryomyolysis and laparoscopic ligations of the uterine arteries, but none of these techniques have significant supporting evidence for clinical use<sup>130,164</sup>.

Multiple randomized controlled trials have shown that fluoroscopy-guided UAE is also an effective intervention for uterine fibroids and has similar complications to surgeries, such as those associated with hysterectomy and myomectomy, but results in a shorter hospital stay as well as less pain immediately following treatment<sup>165,166</sup>. With UAE, embolic particles are placed into the uterine arteries, which results in the ischaemic necrosis of the fibroids but enables the revascularization of the normal myometrium (FIG. 7b). Similar to other uterine-sparing treatments, UAE is associated with an increased risk of subsequent surgical intervention compared with hysterectomy<sup>165,166</sup>.

For women who want to optimize their fertility, findings from a small randomized controlled trial and case series raised the possibility of impaired pregnancy following UAE compared with myomectomy. However, a systematic review concluded that the evidence for this assertion was weak<sup>165,167,168</sup>. In addition, the data obtained on ovarian reserve from a randomized controlled trial showed no significant differences between UAE and hysterectomy in the levels of follicle-stimulating hormone or anti-Müllerian hormone following either procedure<sup>169</sup>.

Other treatment options for women with fibroids who wish to optimize their fertility include MRgFUS. MRgFUS is a non-invasive thermoablative therapy that uses focused ultrasound energy directed through the intact anterior abdominal wall to shrink and soften fibroids (FIG. 7c). Case series suggest sustained symptom relief for up to 5 years following MRgFUS treatment, in addition to successful pregnancy outcomes<sup>170–172</sup>.

**Box 3 | Key unanswered research questions**

- Do certain genes predispose to specific patterns of clinical disease?
- What early life events or exposures either synergize with or cause genetic alterations to produce clinical fibroids?
- What fibroid prevention strategies can be implemented for adolescents and especially young black women?
- What are the biological characteristics of fibroids that inhibit fertility?
- How can the regression pathway be activated in fibroids?
- What genotypes are associated with malignant transformation?

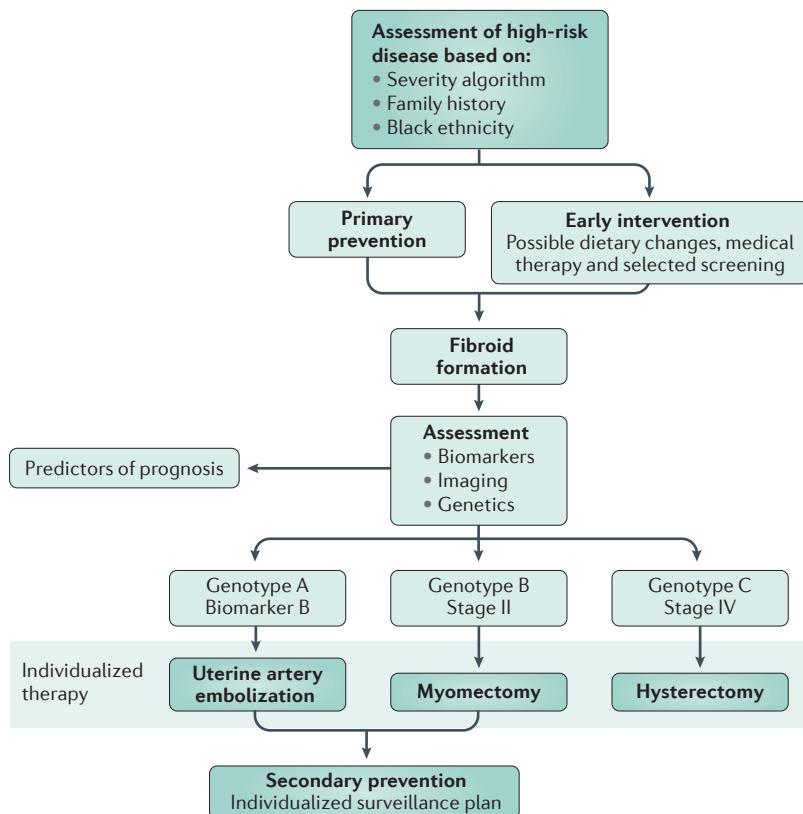
Hysterectomy (FIG. 7d) has long been the mainstay of fibroid treatment in women who no longer intend to get pregnant. However, concerns have been raised regarding the overuse of hysterectomy, as this procedure accounts for three-quarters of all fibroid surgeries in the United States. Although the rates of hysterectomy are decreasing, the lifetime prevalence in the United States is 45%<sup>2</sup>. The main advantages of hysterectomy include the elimination of the risk of the growth of new fibroids, in addition to treating other diseases including adenomyosis and a remarkable improvement in quality of life over the following 10 years<sup>130</sup>. However, long-term health consequences can be associated with hysterectomy, including cognitive impairment and dementia, even with ovarian conservation<sup>173,174</sup>. This area is understudied and requires much further research.

**Quality of life**

Despite the high prevalence of uterine fibroids, few studies have investigated the effects of their symptoms on the health-related quality of life in women. Under-reporting of the functional impairment caused by fibroids is also to be expected, given the sensitive nature of the symptoms and the fact that many women are not aware of effective alternative treatments other than hysterectomy<sup>11,175–177</sup>. Survey data and mixed method research indicate that fibroid symptoms affect work and social life for many women and have a disproportionate effect on black women compared with white women<sup>11,175–177</sup>.

Currently, the only validated questionnaire specific to uterine fibroids is the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) assessment<sup>178</sup>. This instrument includes an 8-item symptom severity subscale, in which higher scores indicate greater symptom severity. Each item is scored on a 5-point Likert scale, so that a raw score of 40 (or a transformed score of 100) indicates maximal symptoms. The symptoms discussed include the distress related to heavy menstrual bleeding, blood clots, urinary frequency and fatigue. The effectiveness of the UFS-QOL questionnaire has been demonstrated in reporting responses following the use of uterine-sparing treatment for uterine fibroids<sup>179</sup>. However, as the UFS-QOL questionnaire reports on menstrual function, it cannot be used to compare hysterectomies with other treatments. The health-related quality of life subscale of the UFS-QOL comprises 29 questions, in which higher scores indicate a better quality of life. This subscale has six component parts regarding concern, activities, energy or mood, control, self-consciousness and sexual function.

Additional validated instruments have been used for specific symptoms associated with uterine fibroids (BOX 2). However, most instruments have not examined the effect of menses on their results, an exception being the recent study using the Female Sexual Function Index<sup>180</sup>. An unmet need exists for improved assessment method for bulk-related symptoms caused by uterine fibroids. The UFS-QOL asks about pelvic tightness and urinary symptoms, but symptoms of bowel dysfunction and abdominal protrusion are difficult to assess<sup>178</sup>.



**Figure 8 | Future concepts of fibroid management.** As information on the correlation of the genotype and phenotype of fibroids becomes available, an individualized approach to the disease can take place. Using a severity algorithm, women at the highest risk could be managed with primary prevention before clinical disease develops. Early intervention might also be possible if risk factors are present and if the disease is mild. Biomarkers or other sources of information could be used to individualize treatment decisions, and secondary prevention could be used for women undergoing uterine-sparing procedures.

#### Treatment to optimize pregnancy outcomes

Fibroids have been reported to contribute to infertility and various adverse pregnancy outcomes<sup>181,182</sup>. However, population-based studies are challenging these assumptions<sup>183</sup>, and the treatment of fibroids to enhance fertility and minimize adverse pregnancy outcomes remains controversial. Most treatment guidelines recommend the treatment of symptomatic fibroids with hysteroscopic myomectomy for FIGO type 0 and type 1 fibroids in women who desire fertility, and some also recommend the use of hysteroscopic myomectomy for the pre-emptive treatment of these fibroids when asymptomatic<sup>130,131,184</sup>. However, conflicting data have been obtained from evidence-based reviews, with some favouring a beneficial

effect of removing submucosal fibroids<sup>185</sup> and others concluding the lack of benefit of this treatment for the optimization of pregnancy outcomes<sup>186,187</sup>.

#### Outlook

The outlook for clinical treatment of uterine fibroids should change markedly in the next decade, which is crucial as the current paradigm for treatment requires modernization. Just as the use of the Halsted radical mastectomy was phased out in favour of lumpectomy, radiation or systemic chemotherapy in the treatment of breast cancer, new research should lead to a paradigm shift in the treatment of uterine fibroids away from hysterectomy<sup>188</sup>. The way forwards is clear; the field needs to move towards determining the predictors of fibroid prognosis and the development of individualized therapies that can be followed by early intervention and both primary and secondary prevention strategies. Ideally, minimally invasive surgical procedures or medical therapies will be more widely used (BOX 3; FIG. 8).

The development of new minimally invasive options for the treatment of fibroids, including both hysteroscopically and laparoscopically deployed radiofrequency ablation, in addition to the use of focused ultrasound therapies can target individual fibroids with minimal morbidity. Furthermore, the use of image-guided therapies or molecularly targeted therapeutics is expected, thus decreasing the morbidity associated with traditional surgical therapies.

Because the transformation of myometrial stem cells into prefibroids seems to be a widespread if not ubiquitous process, future interventions will probably be targeted to the growth acceleration phase of fibroid development. Although we understand some of the genetics underlying fibroid formation, as our understanding of the molecular facets improves, we can expect therapies to emerge that better inhibit growth or that can induce regression. Furthermore, increasing understanding of the biology of this disease will probably enable better diagnosis of malignant and premalignant disease of the uterus<sup>189</sup>.

Finally, uterine fibroids should increasingly be used as a model system for the treatment of malignancies. Indeed, this is the paradigm used as fibroids were selected as the first indication for treatment using MRgFUS; compared with malignant tumours, fibroids are more common, easier to target (because of their larger size) and the consequences of incomplete treatment are minimized. Accordingly, fibroids could serve as a useful model to accurately show the true morbidity of investigational therapies.

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#### Author contributions

Introduction (E.A.S.); Epidemiology (S.K.L.-T.); Mechanisms/ pathophysiology (E.A.S., B.V. and D.V.); Diagnosis, screening and prevention (W.H.C.); Management (E.A.S. and S.L.); Quality of life (E.A.S. and S.L.); Outlook (E.A.S.); Overview of Primer (E.A.S.).

#### Competing interests

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