OPINION PAPER

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The past, present and future of uterine fibroids

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ABSTRACT

Human evolution –specifically the development of bipedalism– altered the shape of the pelvis so that legs alone provided locomotion across the ground. As a result, the forelimbs were freed from locomotion. Though speculative, hands freed from locomotion may have led to the expansion of hand tool use and brain enlargement. With a pelvis no longer optimised for childbirth and with larger fetal brains, childbirth became more challenging. An "obstetrical dilemma" was created. How could large-headed babies be pushed through a narrowed, convoluted pelvis? More uterine muscle, a "neomyometrium," evolved in the uterus, to increase the force of contractions. Because fibroids develop from myometrial tissue, additional fibroids came along with the neomyometrium. Until recently, the fibroid burden that accompanied bipedalism did not become apparent until the advent of modern contraception. Mendelian randomisation studies have demonstrated causal links between women's reproductive histories and their risk of developing fibroids. Multiparity and infrequent menstruation, universally common until only recently, kept this fibroid risk hidden until socio-demographic changes and hormonal contraception unmasked fibroids that evolved with the neomyometrium. Simple therapeutic approaches that (i) periodically and temporarily emulate the clot formation that occurs within the blood vessels of the uterus following childbirth and that (ii) reduce the number of lifetime menstrual cycles may be able to reduce the current high incidence of fibroids.

Keywords: Birth rate, hormonal contraception, Mendelian randomisation, menstruation, myometrium, uterine fibroids

Introduction

In our previous paper,[1] we argued that in distinction from primates and distant hominin predecessors, childbirth in modern day humans requires a large-headed fetus to be propelled by powerful uterine contractions through a narrow, convoluted birth canal. This challenge can be traced back approximately 8 million years, to the evolution of walking and running upright on two feet which freed the forelimbs from climbing. With hands free, our ancestors devised and used tools which required additional computational power leading to the development of the neocortex. Thus, in parallel to the evolution of bipedalism, babies developed with bigger brains and heads (encephalisation) which led to two major problems –a restrictive birth canal and an enlarged fetal head –creating our modern-day obstetrical dilemma: cephalopelvic disproportion.

Among the many compensatory adaptations that permitted successful childbirth in the face of this dilemma, two important changes occurred within the human uterus (Figure 1): (i) through metaplasia and hyperplasia of adjacent connective tissue (mesenchyme), a thick outer myometrial layer,

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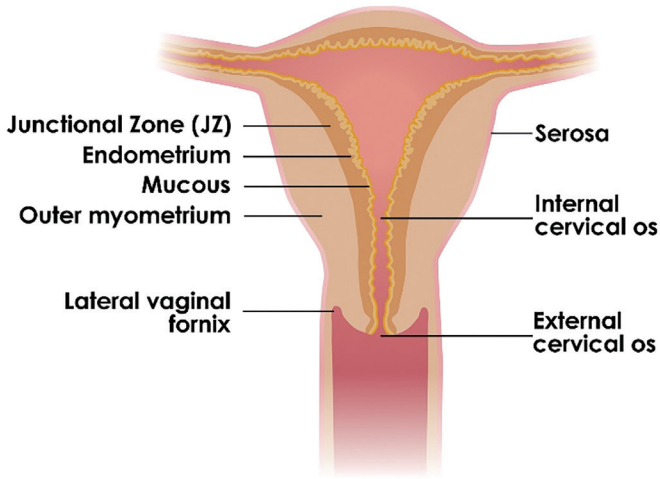

Figure 1. The human uterus-endometrium (yellow), archimetrium or magnetic resonance imaging junctional zone (tan), outer neomyometrium (peach), and serosal (pink) tissue layers. Mucous on the surface of the endometrium is shown in gold. Reproduced by permission from (Burbank).[33]

the neomyometrium, was added like an overcoat, to the archimetrium (junctional zone) and (ii) reflecting the origin of this new tissue, the entire uterus became primarily perfused by the uterine arteries instead of the ovarian arteries. We proposed that the evolution of the neomyometrium was the underlying genetically driven process that led to the high prevalence of fibroids in modern life.[1] How this risk remained hidden for so long, follows.

New fibroids appear from menarche to menopause, consistent with sex hormone-dependent proliferation. Their growth is modulated by progesterone for both cell proliferation and extracellular matrix deposition during the luteal phase of the menstrual cycle while oestrogen plays a supportive role, in part by inducing expression of progesterone receptors.[2] Though other mammals develop fibroids, current prevalence of fibroids in humans is remarkably high. By recent estimate, >75% of women develop fibroids at some point during their reproductive years.[3] Multiple fibroids within the same uterus are clonally unrelated, arising independently from myocytes or stem cells, which account for ~2% of myometrial cells.[4]

The Past

Reproductive Factors and Fibroid Development and Persistence

Fibroids, menstruation, fertility, and childbirth are interrelated. Women with fibroids have a reduced ability to conceive or maintain a pregnancy. Women with few or no prior pregnancies are at heightened risk of developing fibroids. Hence, an inverse relationship exists between parity and fibroid risk. Epidemiologic studies demonstrate that each childbirth leads to a ~20% decrease in fibroid risk, such that in women who have delivered 4 times or more, fibroids are rare.[5] Preterm pregnancies have no overall protective effect, suggesting that the process of term parturition itself, decreases fibroid risk.[6] Parity is inversely related to cumulative number of menstrual cycles, age at menarche, and age of menopause. Over the last 100 years, age of menarche has decreased radically (from 18 in 1840 to 12.7 presently) while age of menopause has only increased modestly (from 48.4 in 1960 to 49.9 in 2018).[7]

Menstruation and Fibroid Initiation

The formation of uterine fibroids including developmental origin and pathogenesis is genetically driven and involves multiple factors operating under certain conditions and circumstances as reported in a comprehensive review.[8] The initiating events and the cell of origin of uterine fibroids remain speculative. Whereas both fibroid and myometrial cells tolerate low levels of ischemia, only fibroid cells are induced to proliferate during hypoxia. This observation has led to the hypothesis that uterine hypoxia, during menstruation, promotes fibroid formation and growth.[9] If so, factors that increase a woman's cumulative number of menstrual cycles (early menarche, delayed menopause, low parity) would be predicted to lead to high fibroid incidence.

The mechanistic link between menstrual history and fibroid risk is somewhat complex. Fibroid development has been proposed to represent a disordered form of wound healing.[10,11] As noted, uterine hypoxia, resulting from vasoconstrictive events during menstruation, may be the original trigger for fibroid formation.[9] Cumulative risk would therefore rise with each menstrual cycle; in the absence of term pregnancies and breastfeeding, the resulting fibroids would be expected to persist and grow throughout a woman's reproductive years. Continuous or extended dosing of progestin-based contraceptives may be another straightforward and potentially helpful intervention to reduce the number of menstrual cycles as will be discussed later.

With menarche at a later age (likely ~18 years), frequent childbirths (5 to 10), and a lifespan too short

for menopause be a consideration, women in ancestral societies probably experienced well under 100 menses in a lifetime and had no fibroids, compared to >400 menses for women today.

Pregnancy Reduces Fibroid Size and Prevalence

Contrary to widely held beliefs, pregnancy is associated with fibroid shrinkage not growth. Small fibroids detected in early pregnancy (<1 cm) typically only grow modestly during pregnancy, while fibroids ≥5 cm tend to shrink significantly, with a mean volume reduction of 2.1% per week.[12]

Parturition Reduces Fibroid Size and Viability

While pregnancy inhibits fibroid growth,[12] childbirth may complete the process by actively shrinking and even eliminating fibroids.[5,6,13-15] In a longitudinal, ultrasound study, Laughlin et al.,[13] demonstrated a general decrease in number and size of fibroid before and after pregnancy. This effect however, is neither universal nor linear since large or well-established fibroids frequently persist.

Fibroid devitalization following childbirth is best explained by widespread clot formation throughout the uterus and its adjacent arteries and veins following separation of the placenta away from the uteroplacental bed during vaginal or Caesarean delivery.[5,16] Following placental separation, clotting occurs quickly and widely throughout the uterine circulation and in adjacent veins, creating transient total uterine ischemia that affects fibroids as well as healthy myometrium. In healthy myometrium, the duration of this effect is short-lived; clots are degraded in a wave of fibrinolysis that peaks 3 hours post-partum.[17] Perfusion is thus restored to the uterus and it survives. Fibroids, on the other hand, which are not capable of efficient fibrinolysis, they devitalise and shrink.[5,16] At the extreme, fibroid degeneration and expulsion from the uterus following childbirth is well documented.[18]

The Present

Lifetime parity has declined steadily, worldwide, with a mean total fertility falling from 5.29 in the 1960s to 2.74 after 2010[19] and the total fertility rate (TFR) is now well under the stable replacement rate of 2.1 children per woman.[20,21] These trends show no sign of abating.[20,21] Extreme examples of low birth rate have been seen in economically advanced countries, notably Japan and South Korea. A similar pattern is evident in other countries; by 2100, only 6 countries are expected to maintain a fertility rate above maintenance. Projections indicate that the global population is likely to peak well before the end of the century and subsequently decline towards a TFR <1.5.[20,21]

As might be anticipated, recent surveys indicate that fibroids have become increasingly common globally,[3] with prevalence increasing 79% between 1990 and 2019. Mendelian randomisation studies confirm that reproductive factors like reduced parity and increased cumulative number of menstrual cycles contribute to this trend.[22,23] From studying isolated modern societies with unrestricted reproduction, it appears women's lifetime parity was likely between 5 and 10 live births reducing fibroid risk by 20% with each birth.[5,6] Postpartum clearance of fibroids, in response to clotting within the uterine vasculature, may be similar to the response of fibroids following uterine artery embolization/occlusion (UAE/UAO), medical procedures used to treat women with symptomatic fibroids.[5,16]

Which Came First, Fibroids Causing Decreased Fertility or Childbirth Devitalizing Fibroids?

It is not immediately clear which is cause and which effect. Do fibroids cause women to be less fertile, or are women who have few children predisposed to develop fibroids? To address this longstanding question, two groups have applied Mendelian randomisation to extract causal information from large databases. Mendelian randomisation begins by conducting genome-wide association studies, to identify genomic loci where polymorphisms are statistically associated with traits of interest (e.g., age at first birth, total number of births, and age at menarche and menopause) as well as their history of fibroids.

The same analysis can also be run in reverse, to ask if genetically predicted high risk of fibroids might be causally linked to genetically predicted early age of first birth (AFB)—another formally possible outcome. Causal findings derived from one database can also be re-examined in another database, to confirm the identify of genes of interest and to ask whether the causal arrow points in a consistent direction across different study populations.

Using Mendelian randomisation approach, Xiao et al.[22] found that two parameters that correspond to higher numbers of menstrual cycles (i.e., early menarche and late menopause) were each significantly and causally linked to higher likelihood of fibroids. Higher AFB likewise

predicted increased fibroid risk. These conclusions were based on analysis of large cohorts such as the publicly available FibroGENE consortium, with clinical and genetic data for approximately 300,000 women, predominantly of European ancestry.[22] Independently, Wang et al.[23] used a similar approach to look at reproductive parameters, using both the FibroGENE and a second large database from the FinnGen consortium, representing approximately 190,000 women. Their causal analysis reached similar conclusions: Genetically predicted early menarche and late menopause—both associated with increased numbers of menses—caused increased fibroid risk.[22,23] They also noted a remarkable 4-fold reduction in fibroid risk in women with higher numbers of live births; this effect was consistent and significant in each of databases analyzed.[22,23]

Both groups tested the reverse causal claim, whether fibroid risk might be causally linked to reproductive parameters like early or late AFB. In general, no such link was found, suggesting that the causal arrow points from women's reproductive history (e.g., many life-time menstrual cycles, delayed AFB, and fewer pregnancies) to high incidence of fibroids, and not in the reverse direction.[22,23] However, Wang et al.[23] found one interesting exception– a weak but significant finding that fibroids cause a reduced lifetime number of childbirths, implying that fibroids are also causally linked to reduced fertility. It must be pointed out however, that although Mendelian randomisation data predominantly support genetic predisposition as the primary driver of fibroid risk, the reproductive traits may act as modifiers rather than evidence of true bidirectionality.

Maternal Age at First Birth

Since the 1960s, in addition to reducing the number of children, couples have also chosen to delay the age of having a family trending to an increased AFB.[24] For example, in the US, the group of women with the largest share of first births in 1960 was 20 to 24 years old (43%). By 1990, the share experiencing a first birth among this age group had declined to 31%, but it was still the most common age group. In 2018, first births among women occurred most often between ages 25 to 29 (29%).[24] In Canada, the average age of first-time mothers increased from 23.2 years to 29.4 years between 1959 and 2019, rising to 31.6 years as of 2022.[25] Age at first birth limits parity and is related to more menstrual cycles both of which lead to increased fibroid risk.

The Future

Epidemiological and Mendelian randomisation studies support a causal basis of the well documented inverse relation between parity and fibroid risk.[5,6,14-17,22,23] In general, the more children a woman has, the fewer fibroids she is likely to face. Conversely, the fewer children she has, the more fibroids she is likely to experience. To emulate the biological process that devitalizes fibroids during childbirth, uterine ischemia and clot formations can be created with a transvaginal, Doppler-guided vascular clamp that causes temporary UAO.[26] Because this clamp system is temporary (<6 hours) and minimally invasive, such a procedure might be used, periodically, to substitute for the fibroid devitalizing effects of natural childbirth.

The Ambiguous Role of Hormonal Contraception

Widespread use of hormonal contraception dates from the 1960s in Western countries. Despite the complexity of the literature on contraception and fibroids, most studies report reduced fibroid prevalence in women with a history of oral contraceptives,[6] levonorgestrel intrauterine systems (LNG-IUS),[27] levonorgestrel implants[28] or depo-medroxy-progesterone acetate (DMPA).[29-32] A systematic review reported that prior use of oral contraceptives was a protective factor for uterine fibroid risk.[6] In general, oral contraceptive use reduced fibroid risk with prolonged utilization by approximately 30% after 5 to 10 years. Use of oral contraceptives at young ages was reported to be associated with an elevated risk in at least one study.[6] Presently, even when oral contraceptives are packaged with 4–7 days of placebo pills per month, some women and caregivers recommend taking the active pills without interruption, thus avoiding regular monthly withdrawal bleeding. In addition, some oral contraceptive products are now available that are designed for uninterrupted, year-long daily dosing; various other contraceptive regimens and devices have long been available that lead to continuously suppressed menstruation.

LNG-IUS produce an extended state of amenorrhea or oligomenorrhea and may limit the development of new fibroids. In a multicenter, prospective 7-year randomized controlled trial in USA and Canada, the LNG-IUS reduced the incidence of bleeding and, in the long-term, of myoma and myoma-related surgery in comparison with the copper-T intrauterine device. Among TCu380 users, incidence of fibroids increased significantly with time, notably so after 5 years of use (P<0.001), and with age at admission (P<0.05). No myoma

or enlarged uterus required surgery in LNG-IUS group. Five women in TCu380 had myomectomy and 1 woman had hysterectomy.[27] Similar effect has been reported in chimpanzees in captivity. Compared to females with non-hormonal or no contraception, those with levonorgestrel implants had significantly reduced fibroid risk, both in parous (P<0.03) and nulliparous (P<0.04) animals.[28]

Four studies have reported a significant reduction in fibroid risk with long-term treatment with DMPA.[29-32] Current use of DMPA was associated with approximately 50% reduction in risk. Harmon and Baird[31] reported that participants exposed to DMPA within the previous 2 years experienced reduced leiomyoma development during the subsequent observation interval compared with never users, including lower leiomyoma incidence (5.2% vs. 10.7%), adjusted hazard ratio: 0.6 [95% confidence interval (CI): 0.4–1.0], 42.0% lower leiomyoma growth (95% CI: 251.4 to 230.7) and 60% greater leiomyoma loss (adjusted risk ratio 1.6, 95% CI: 1.1–2.2). Excess leiomyoma loss was also seen for those who used DMPA 2-4 years before the visit compared with never users, 2.1-fold increase (95% CI: 1.4–3.1).[32]

However, the apparent protective effect of progestin-based contraception against incident fibroids remains puzzling given the essential role of endogenous progesterone for fibroid initiation and development.[2] Given the rapid evolution of fibroid therapeutics, including the use of specific progesterone receptors modulators and gonadotropin releasing hormone agonists and antagonists, all of which have been effective in short-term treatment of symptomatic fibroids, we found no evidence that any of these agents prevents formation or decreases the incidence of fibroids. Further research may shed light on the impact of these therapeutic molecules on fibroid development.[33]

Conclusion

To walk and run on the ground, the human pelvic skeleton became narrow and convoluted. At the same time, fetal brains and heads became larger. To push a large-headed baby through a convoluted pelvis, myometrium enlarged. The enlargement carried with it a silent, hidden, high risk of fibroids. The risk remained latent for millennia, due to high parity and few lifetime menstrual cycles. Modern family planning has resulted in smaller families and has unmasked the latent, increased fibroid risk of the neomoymetrium (Figure 2). Given modern demographic realities, fibroid prophylaxis (methods to decrease the number of menstrual

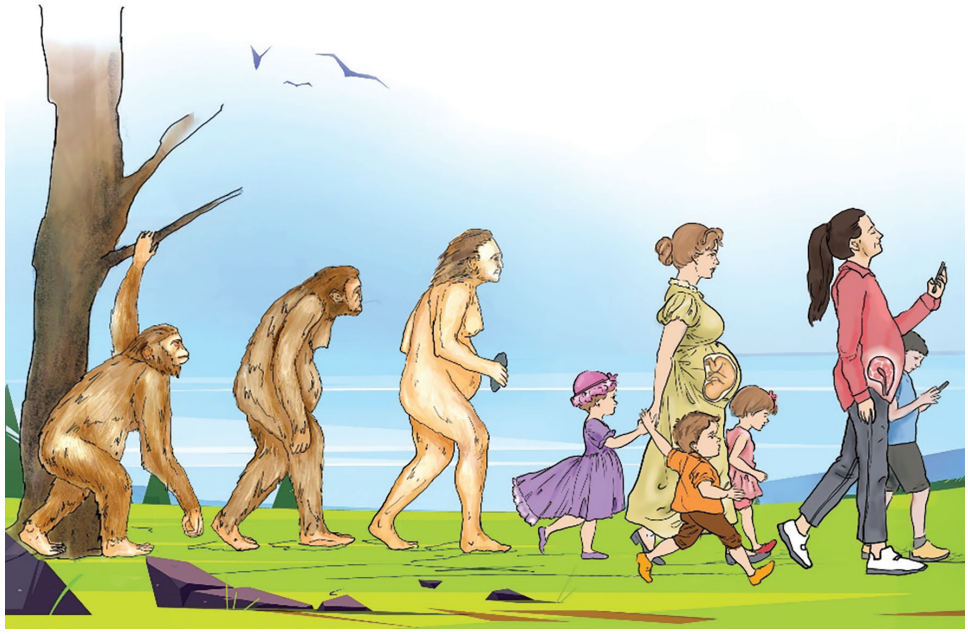

Figure 2. The ascent of modern woman. Family size has declined substantially in recent decades, as birth control has allowed women to delay or opt out of pregnancy. As a result of increased average age at first pregnancy and wider spacing between pregnancies, it is now common for women to experience a nearly uninterrupted series of menstrual cycles from menarche to menopause—an atypical pattern for women in prehistory and even in recent history. Among the possible physiological consequences of this change is an increase in the frequency of uterine fibroids. We propose that a high risk of fibroids was always present for humans, although in latent form, and that this risk has been unmasked as women experience more menstrual cycles and fewer pregnancies. Original art courtesy of Ms. Deepti Saxena (Kasaza Art and Design, Toronto, Ontario, Canada). Image size: 1063 × 709 px (72 dpi).

cycles and methods to emulate the biology of childbirth) may become priorities in women's healthcare.

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