

Research Article

UTERINE MYOMA, IS IT ONLY CAUSED BY ESTROGEN?

* I GdeSastra Winata and William Alexander Setiawan

Obstetric and Gynecology Department, Sanglah General Hospital, Indonesia.

Received 15th November 2022; Accepted 16th December 2022; Published online 30th January 2023

ABSTRACT

Introduction: Uterine myomas are the most common benign neoplasms of the female reproductive tract and a major public health concern in reproductive age women. Uterine myomas are made of abnormal smooth uterine muscle cells and fibroblasts surrounded by extensive amount of extracellular matrix (ECM). However, other very important pathways exist, which are not only hormone-dependent. So we would like to make a systematic review to know what the causes of uterine myoma are. **Methods:** We performed a Google scholar search of papers published from 2017 until 2021, using the Medical Subject Heading terms "uterine myoma" or "leiomyoma" combined with "hormone" or "estrogen" or "factor" or "risk factors" and free search terms "hormone" or "estrogen" in combination with "fibroids" or "uterine fibroids" or "myoma" or "uterine myoma" or "leiomyoma" or "uterine leiomyoma". **Result and Discussion:** We identified 146 potentially relevant citations. Based on the title and abstracts, full texts of 23 articles were selected for detailed evaluation. Of these articles, 12 articles were excluded. The remaining 11 articles met our criteria and were therefore included in the analysis. **Conclusion:** Uterine myoma is caused by multifactorial. Besides of Estrogenic, there are many factors that can increase of uterine myoma percentages. The other factors are age between 30-50 years old, the inflammatory process in uterus, vitamin D deficiency, air pollution, alcohol consumption, body mass index > 25, the concentration of MCM protein and CYP1A1 gene.

Keywords: uterine myoma, fibroid, risk factors.

INTRODUCTION

Uterine Myoma are the most common benign neoplasms of the female reproductive tract and a major public health concern in reproductive age women. The overall incidence of those lesions is hard to determine as there are only few well performed studies. However, in some populations, it may even reach 70% of women [1]. Although most women with Uterine myoma are asymptomatic, over 30% of them will present with various symptoms. Uterine Myoma cause significant morbidity and may compromise daily activities, relationships or workplace performance [2,3]. Uterine Myoma are made of abnormal smooth uterine muscle cells and fibroblasts surrounded by extensive amount of extracellular matrix (ECM) including collagens, fibronectin, laminins, and proteoglycans [4,5]. One of the most important things about uterine myoma is their tendency to grow, which depending on the location, may cause clinical symptoms. The incidence of uterine myoma is increase in the United States. It said the incidence is 2-12.8 people by 1000 women each year [6]. Research that has been done in Nigeria (Department of Gynecology, University of Nigeria) found that the prevalence of uterine myoma was 9.8%. Whereas research in Indonesia in 2008 found uterine myoma around 19.8%, and in 2009 was 11.70% [7]. Also from the other studies getting 2.39%-11.70% [8]. According to research in the gynecology from Hospital Dr. Margono Soekardjo Purwokerto prevalence of uterine myoma reached 63.0% [9]. Complex signaling pathway alterations are crucial for uterine myoma development, but the exact underlying biology of uterine myoma is unclear. The topic of the pathophysiology of uterine myoma focuses mostly on steroids and other hormones [4,10]. However, other very important pathways exist, which are not only hormone-dependent. So we would like to make a systematic review to know what the causes of uterine myoma are.

METHOD

We performed a Google scholar search of papers published from 2017 until 2021, using the Medical Subject Heading terms "uterine myoma" or "leiomyoma" combined with "hormone" or "estrogen" or "factor" or "risk factors" and free search terms "hormone" or "estrogen" in combination with "fibroids" or "uterine fibroids" or "myoma" or "uterine myoma" or "leiomyoma" or "uterine leiomyoma". Studies were included if they fulfilled the following criteria: a) case-control or cohort studies, reporting original data; b) studies reporting information on the association between hormonal and myoma, and/or estimates of the relative risk (RR) or the odds ratio (OR), with the corresponding 95% confidence intervals (CI), or frequency distribution to calculate them; c) studies where diagnosis of myoma was ultrasound or histological confirmed and/or clinically based. The exclusion criteria were: a) cross-sectional studies, since in this study design exposure and disease are recorded at the same time and it could not determine whether the exposure preceded the occurrence of uterine myoma, unless the studies included only newly-diagnosed myoma cases; b) studies where myoma diagnosis was exclusively self-reported.

RESULT

We identified 146 potentially relevant citations. Based on the title and abstracts, full texts of 23 articles were selected for detailed evaluation. Of these articles, 12 articles were excluded. The remaining 11 articles met our criteria and were therefore included in the analysis.

From the 11 articles we make a review about all the factors that can possibly increase the risk of uterine myoma. Besides estrogen, there are several pathways for the formation of uterine myomas in addition to hormonal factors:

*Corresponding Author: I Gde Sastra Winata

Obstetric and Gynecology Department, Sanglah General Hospital, Indonesia.

Age

Age has a complex effect on the growth of uterus fibroids. The research has been done by Qingxiu L, *et al.*, in 2021, said the incidence of fibroids are rare in women younger than 20 years of age, but women aged 30–50 have a higher prevalence of uterine fibroids. After the age of 50 years, uterine fibroids may shrink. The age range in the logistic regression model was 20–55 years. Beyond this range, the influence of age on uterine fibroids appeared uncertain. Qingxin L, *et al.*, found that before the age of 20 and after the age of 50, hormone levels are significantly lower than during the childbearing years. Therefore, the uterus grows the fastest during the reproductive years.[11]

Inflammatory Process

Some investigators suggest that uterine myoma arise as a consequence of a chronically active inflammatory process with the cytokines responsible for uterine myoma-associated symptoms, such as pain, abnormal uterine bleeding, and infertility. Inflammation stimulates myofibroblasts to over express extracellular matrix (ECM), which results in a disorganization of ECM components, with an aberrant presence of two collagen subtypes, fibronectin and proteoglycans [12]. Additionally, numerous studies indicate that the deposition and accumulation of ECM in uterine myoma are regulated by growth factors, cytokines, and steroid hormones; ECM, in turn, sequesters growth factors to promote its own stability as well as to limit their activity. This fibrotic response is induced by the recruitment of inflammatory cells, which, by releasing inflammatory signals, overstimulate myofibroblasts to produce ECM, resulting in pathological fibrosis [13].

Vitamin D Deficiency

Vitamin D is a group of steroid compounds with a powerful impact on many parts of the human body. This vitamin is believed to regulate cell proliferation and differentiation, inhibit angiogenesis, and stimulate apoptosis. Nowadays, hypovitaminosis D is believed to be a major risk factor in the development of uterine myoma. In many studies vitamin D appears to be a powerful factor against uterine myoma, resulting in the inhibition of tumor cell division and a significant reduction in its size, however, the exact role of this compound and its receptor in the path physiology of uterine myoma is not fully understood. According to available studies, vitamin D and its analogs seem to be promising, effective, and low-cost compounds in the management of uterine myomas and their clinical symptoms, and the anti-tumor activities of vitamin D play an important role in uterine myoma biology. The synergy between vitamin D and selected anti-uterine myoma drugs is a very interesting issue that requires further research [14].

Air Pollution

Air pollution is one of the leading causes of death. Exposure to air pollutants affects vital cellular mechanisms and is intimately linked with the etiology of many chronic diseases. Air pollution, including PM2.5, results in infertility, menstrual irregularity, and endometriosis. In addition, chronic exposure to PM2.5 is associated with the incidence of clinically symptomatic uterine myoma. A 10-year cohort-based case-control study including 11,028 Taiwanese women diagnosed with uterine myoma suggested that exposure to PM2.5 and O3 may increase the risk of developing uterine myoma [15]. However, only limited studies have investigated the relationship between air pollution and uterine myoma development; therefore, more studies are needed to confirm these findings in other populations.

Alcohol Consumption

Nurses' Health Study II revealed the positive association between current alcohol consumption and risk of uterine myoma [16,17]. The Black Women Health Study concluded that uterine myoma risk among African American women is positively correlated with past and current alcohol intake [18]. In a study involving 133,000 female teachers and school administrators, drinking at least 20 glasses of alcohol per day was significantly associated with an increased risk for uterine myoma [19]. Alcohol intake also altered the growth factors and cytokines, which play a critical role in uterine myoma pathogenesis. Moreover, alcohol-induced DNA damage might be a contributor. Acetaldehyde, an endogenous and alcohol-derived metabolite, caused DNA damage, particularly double-stranded breaks, that, despite the activation of recombination repair, resulted in chromosomal rearrangements in stem cells [20].

Body Mass Index

From the research has been done by C. Amruta, *et al.*, in 2020, the body mass index is also playing a role in the uterine myomas. From the research, out of 100 women studied 63 were nulliparous and 37 women were multiparous. Incidence of fibroid is inversely proportional to parity. When BMI 25, 57 women had fibroids and BMI between 18-25 group, 37 women were diagnosed with fibroid. So the researcher concluded, there is a directly proportional association with BMI. Greater the BMI the more was the risk of fibroids.[21]

MCM protein

The MCM (minichromosomal maintenance) protein family consists of peptides whose primary function is participation in the molecular mechanism of creating replication forks while regulating DNA synthesis. Research by Rubisz, P in 2020, found that statistically significant stronger expression of all the investigated MCMs was observed in uterine myoma patients, as compared to the control group. In addition, moderate and strong positive correlations were also found between all tested proliferative markers. The expression of the MCM-7 protein also correlated positively with Estrogen and Progesterone. With regard to clinical and pathological data, there was a negative correlation between the expression of MCMs and the number of both pregnancies and births. Significant reductions in MCM-5 and MCM-7 expression were observed in the group of women receiving oral hormonal contraceptives, while smoking women showed an increase in MCM-7, Estrogen, and Progesterone.[22]

CYP1A1 enzyme

CYP1A1 is a CYP450 enzyme, the main enzyme involved in the catabolism of estrogen. CYP1A1 is one of three members of the CYP1 family that is involved in the metabolism of a large number of xenobiotic. Research that done by Bella S, A, *et al.*, in 2020, found that genotype polymorphisms and the CYP1A1 gene allele (Ile462Val) are associated with the incidence of uterine myoma against ethnic Malays in South Sumatera. But the researcher said, the contribution of CYP1A1 itself varies between each population because it is also influenced by many things including the presence of the hormone estrogen, and the interaction of genes with environmental factors. Polymorphisms in the CYP1A1 gene (Ile462Val) are a risk factor for uterine myoma in Chinese, Iranian, German women due to any change in enzymatic activity.[23]

CONCLUSION

Uterine myoma is caused by multifactorial. Besides of Estrogen, there are many factors that can increase of uterine myoma percentages. The other factors are age between 30-50 years old, the inflammatory process in uterus, vitamin D deficiency, air pollution, alcohol consumption, body mass index > 25, the concentration of MCM protein and CYP1A1 gene.

REFERENCES

1. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG* 2017; 124:1501–1512.
2. Al-Hendy A, Myers ER, Stewart E. Uterine fibroids: burden and unmet medical need. *SeminReprod Med* 2017; 35:473–480.
3. Gracia M, Carmona F. Uterine myomas: clinical impact and pathophysiological bases. *Eur J ObstetGynecolReprodBiol* 2020. Epub. Jan 30;S0301- 2115(20)30052-X.
4. Bulun SE. Uterine fibroids. *N Engl J Med* 2013; 369:1344–1355. 9. && Islam MS, Ciavattini A, Petraglia F, et al.
5. Extracellular matrix in uterine leiomyoma pathogenesis: a potential target for future therapeutics. *Hum Reprod Update* 2018; 24:59–85.
6. Kang dkk, 'Up-regulation of Apoptosis by Gonadotrophin-releasing Hormone Agonist in Cultures of Endometrial Cells from Women with Symptomatic Myomas', *Human Reproduction*, 2010.
7. Okezie; Ezegwui, H.U, 'Management of Uterine Fibroids in Enugu, Nigeria', *Journal ObstetricGynaecology* 26(4), 2006.
8. Devy, IL; Sudiat, Muhammad; Basuki, Rochman, 'HubunganFaktorRisikodanKejadianMioma Uteri di RSUD Tugurejo', *JurnalKedokteranMuhammadiyah*, Vol 1, No1, Semarang, 2012.
9. W ,Qonita; AS, Islimsjaf; Adityono, 'HubunganHiperplasiaEndometrium DenganMioma Uteri: StudiKasusPadaPasiendGinekologi RSUD Prof. Dr. MargonoSoekardjoPurwokerto'. *Mandala of Health*, Volume 5, Nomor 3, JawaTengah, 2011
10. Borahay MA, Asoglu MR, Mas A, et al. Estrogen receptors and signaling in fibroids: role in pathobiology and therapeutic implications. *ReprodSci* 2017; 24:1235–1244
11. Qingxiu Li, JiehuiZhong, Dongyi Yi, et al. Assessing the risk of rapid fibroid growth in patients with asymptomatic solitary uterine myoma using a multivariate prediction model. *Ann Transl Med.* 2021 Mar; 9(5): 370. doi: 10.21037/atm-20-4559
12. Cetin E, Al-Hendy A, Ciebiera M. Non-hormonal mediators of uterine fibroid growth. *CurrOpinObstetGynecol* 2020;32:361–70
13. Islam MS, Ciavattini A, Petraglia F, Castellucci M, Ciarmela P. Extracellular matrix in uterine leiomyoma pathogenesis: a potential target for future therapeutics. *Hum Reprod Update* 2018;24:59–85.
14. Ciebiera M, Wlodarczyk M, Ciebiera M, Zareba K, Lukaszuk K, Jakiel G. Vitamin D and Uterine Fibroids-Review of the Literature and Novel Concepts. *Int J Mol Sci.* Jul 14 2018;19(7)doi:10.3390/ijms19072051
15. Lin CY, Wang CM, Chen ML, Hwang BF. The effects of exposure to air pollution on the development of uterine fibroids. *Int J Hyg Environ Health.* Apr 2019;222(3):549-555. doi:10.1016/j.ijheh.2019.02.004
16. Takala H, Yang Q, El Razek AMA, Ali M, Al-Hendy A. Alcohol Consumption and Risk of Uterine Fibroids. *CurrMol Med.* 2020;20(4):247-258. doi:10.2174/1566524019666191014170912
17. Chiaffarino F, Cipriani S, Ricci E, et al. Alcohol consumption and risk of uterine myoma: A systematic review and meta analysis. *PLoS One.* 2017;12(11):e0188355
18. Wise LA, Palmer JR, Harlow BL, et al. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. *Hum Reprod.* Aug 2004;19(8):1746-54. doi:10.1093/humrep/deh309
19. Templeman C, Marshall SF, Clarke CA, et al. Risk factors for surgically removed fibroids in a large cohort of teachers. *FertilSteril.* Oct 2009;92(4):1436-1446. doi:10.1016/j.fertnstert.2008.08.074
20. Garaycochea JI, Crossan GP, Langevin F, et al. Alcohol and endogenous aldehydes damage chromosomes and mutate stem cells. *Nature.* Jan 11 2018;553(7687):171-177. doi:10.1038/nature25154
21. C., Amruta, et al. Association between uterine leiomyoma with body mass index and parity in the women of coastal Karnataka, India. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, vol. 9, no. 2, Feb. 2020, pp. 740+. Gale OneFile: Health and Medicine, link.gale.com/apps/doc/A652737763/HRCA?u=anon~bcfb5491&sid=googleScholar&xid=eaaa0d53. Accessed 19 Dec. 2021.
22. Rubisz, P.; Hirnle, L.; Kobierzycki, C. The Immunohistochemical Expression of MCM-3, -5, and -7 Proteins in the Uterine Fibroids. *Curr. Issues Mol. Biol.* 2021, 43, 802-817. <https://doi.org/10.3390/cimb43020058>
23. Bella R A, Ferry Y, Legiran. Polymorphism of CYP1A1 (Ile462Val) Gene Related to Uterine Myoma in Malays Ethnicity of South Sumatera. 2020. *MutiaraMedika: JurnalKedokteranKesehatan.* Vol 20 No 2 Page 92-97
