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Systematic Review

Uterine fibroids and infertility: a controverse but concrete link

Radmila Sparić[1,2,*], Mladen Andjić[1], Lazar Nejković[2,3], Jelena Štulić[3], Aleksandar Dmitrović[1,2], Radomir Aničić[2,3], Zagorka Milovanović[2,3] , Đina Tomašević[4], Andrea Tinelli[5,6,7]

[1]Clinic for Gynecology and Obstetrics, University Clinical Centre of Serbia, 11103 Belgrade, Serbia
[2]School of Medicine, University of Belgrade, 11103 Belgrade, Serbia
[3]Clinic of Gynecology and Obstetrics, Narodni Front, 11103 Belgrade, Serbia
[4]University Clinical Centre of Serbia, 11103 Belgrade, Serbia
[5]Department of Obstetrics and Gynecology and CERICSAL (CEntro di RIcerca Clinico SALentino), "Veris delli Ponti Hospital", 73100 Lecce, Italy
[6]Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Vito Fazzi Hospital, 73100 Lecce, Italy
[7]Laboratory of Human Physiology, Phystech BioMed School, Faculty of Biological & Medical Physics, Moscow Institute of Physics and Technology (State University), 141700 Dolgoprudny, Russia
*Correspondence: radmila@rcub.bg.ac.rs (Radmila Sparić)
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Abstract

Background: Uterine fibroids (UFs) are the most common female benign tumors linked to significant morbidity. There are large literature data connecting UFs with infertility and adverse pregnancy outcome. In this research, authors reviewed literature on UFs, analyzing their relationship with infertility, influence of different therapeutic approaches of UFs on fertility and the possible mechanisms related to UFs and infertility. **Methods**: MEDLINE and PubMed search, during the years 1990–2020 was performed using a combination of keywords on such topic. Peer-reviewed, systematic review, meta-analysis and prospective trials, examining relationship between UFs and infertility were included in this investigation. According to authors evaluation, additional articles were also identified from the retrieved papers references and included in this narrative review. **Results**: UFs, especially the submucous and intramural types, with related treatments are linked to impairment of fertility and adverse pregnancy outcome, but many data are conflicting. Molecular mechanisms investigations could explain relationship between UFs and infertility. **Conclusion**: UFs are linked to infertility and interventions improve fertility. However, many studies conflict in the final results, so further investigations on UFs and infertility should clarify the exact role of molecular mechanisms of this association.

Keywords: Uterine fibroids; Leiomyomas; Fertility; Pregnancy; Myomectomy; *In vitro* fertilization; Pregnancy rate

1. Introduction

Although uterine fibroids (UF) or leiomyoma represents the most common benign tumors in women of reproductive age, their pathophysiology as well as mechanism included in their onset are still unclear [1]. UF could have a negative impact on reproductive system and could be important causing factor of morbidity [2]. The women with UFs experience usually heavy or prolonged menstrual bleeding, which can lead to iron-deficiency anemia and social embarrassment. Other symptoms caused by an enlarged myomatosic uterus are abdominal distension, pain, gastrointestinal symptoms (such as diarrhea or constipation) and urinary symptoms (such as urinary frequency, urinary retention or nocturia). On the other hand many women remain asymptomatic regardless UF size [3]. The UFs management represent great economic and public health issue, which include not just treatment of UF "per se", such as treatment of UF related issues as well as infertility, pregnancy achievement and maintenance [4].

One of the main problems in UFs pathophysiology is its correlation to fertility and pregnancy. In some women, UF can lead to difficulties to achieve pregnancy and terms of pregnancy course. On the other hand, a significant proportion of women with UF get pregnancy and deliver without difficulties [2]. It is very important to have in mind that not just UF, but also different method of treatments could diminish fertility in women with UF.

The aim of this narrative review is to present relationship between UF and infertility, influence of various therapeutic approaches of uterine fibroid on fertility and possible mechanisms which link UFs and infertility.

2. Methods and materials

Authors investigated the available data on UFs and infertility, by a MEDLINE and Pub Med search, during the years 1990–2020, using a combination of keywords, such as "myoma", "leiomyoma", "fibromyoma", "leiomyofibroma", "fibroleiomyoma", "uterine fibroids", "myomectomy", "pregnancy rates", "live birth", "miscarriages", "pregnancy", "implantation rate" and "infertility". Randomized controlled studies were used when available; otherwise, the most relevant literature on this

topic was included basing on authors' evaluation. Peer-reviewed articles regarding myomas, UFs and leiomyomas were included in this manuscript. Additional articles were identified from the references of relevant papers. The terms: "leiomyomas", "uterine fibroids", "fibromyomas", "leiomyofibroma" and "fibroleiomyomas" can also be found in the literature describing UFs.

3. Uterine fibroids etiopathogenesis, epidemiology, biology and genetics origin

Even though UFs have significant role in women population morbidity, the exact mechanisms causing their onset and growth are yet to be fully understood. There is broad spectrum of theories which explained pathophysiological mechanism of UFs [5]. UFs represent monoclonal tumors as they develop from a single myometrial cell which transform into UF cell. Further development of UF include production and accumulation of an extracellular matrix by clonal cell [3,5]. The UFs growth depends on steroid hormones, dominantly on progesterone. The progesterone modulates UF growth by an increase of expression of genes associated with cytokines and individual growth factors [5].

Epidemiological risk factors for UFs onset and development are age, race, body mass index, sex hormones, heredity, life habits (including smoking, stress, physical activity, caffeine and alcohol consumption, diet rich in red meat and soy), environmental pollutants, as well as the chronic disease, such as hypertension and diabetes [3,6].

As for everyone multifactorial conditions, for which is not determined accurate mechanism of development, it has been considered that gene polymorphism have a large role in UFs onset and development [7]. According to the results of a genome-wide association scan (GWAS) study, the UFs development is determined by two groups of genes. First group comprise genes involved in genome stability such as are: *TERT, TERC, OBFC1*, *TP53* and *ATM* and a second group, including genes involved in the development of genitourinary system such as are: *WNT4, WT1, SALL1, MED12, ESR1, GREB1, FOXO1, DMRT1* and uterine stem cell marker antigen *CD44* [7].

Epigenetic control and proteomic plays, as well as local growth factors, neuropeptides and neurotransmitters also a significant role in the UF pathogenesis [8]. Modification of histone and DNA methylation are epigenetic mechanisms regulating the expression of genes independent from the DNA sequence of the genome [9].

4. Uterine fibroids and infertility

In order to define the exact relationship between UFs and infertility, it should be performed randomized clinical trial (RCT) and compare clinical pregnancy rate (CPR), to recognize any differences in time to achieve pregnancy between women wishing pregnancy, with and without UFs. Literature currently lacks of such studies. Available studies on infertile women in whom other infertility causes, apart from UF, have been ruled out, undoubting indicate beneficial effects of myomectomy in terms of PR and pregnancy outcomes [10].

Bulletti *et al*. [10] conducted a prospective randomized study to investigate the effect of UFs and their surgical removal on PR in infertile women. The authors compared 106 patients with UFs who underwent laparoscopic myomectomy and 106 patients who did not, with 106 patients with unexplained infertility without UFs. The lowest PR were observed from women with untreated UFs (11%). Overall PR were higher in women who underwent myomectomy (42%) in comparison to these without UFs (25%). The delivery rates were significantly higher in women who had myomectomy (42%) than in those who did not (11%). Further, patients who did not undergo myomectomy had significantly fewer deliveries than those who didn't have UFs.

Another important unsolved questions, in the field of reproductive medicine, if UFs have an overall negative effect on female fertility, if all UFs should influence fertility and, finally, if UF size and position should influence female fertility and, eventually, what are the related mechanisms.

It has been observed that women who underwent myomectomy exhibited an overall higher PR than patients without surgical treatment. Differences were statistically significant only in those with submucosal and intramural UFs, with a submucosal component. Miscarriage rates (MR) were highest in women without myomectomy. Concerning their results, it is noteworthy that patients with subserosal UFs were not surgically treated. Thus, myomectomy positively influenced the MR in most of the groups [11].

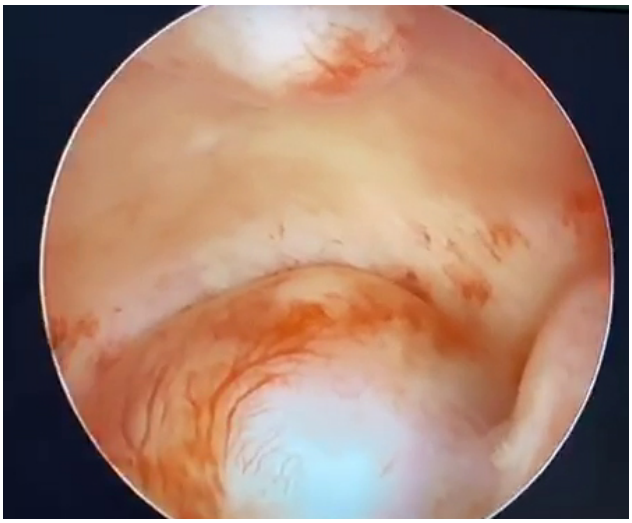

Fig. 1. Hysteroscopy of submucosal uterine fibroid.

Most of the researchers concur that submucosal UFs impair fertility, while the issue of intramural and subserosal UFs impact is more complex to define. There are many theories explaining the influence of submucosal UFs on fertil-

ity: they distort the shape and size of the uterine cavity, altering uterine peristalsis, interfering with sperm migration and ovum transport [12]. Moreover, this possibly makes the endometrial surface less suitable for implantation [12]. Furthermore, by causing frequently irregular menstrual bleeding, submucous UFs reduce the frequency of coitus. Focal changes in endometrium caused by UFs presence, i.e., inflammation, vascular disturbance, secretion of vasoactive substances and altered environment may also cause nidation failure and gestation discontinuation [12]. Hysteroscopy of submucosal uterine fibroid is shown in Fig. 1.

Yoshino *et al.* [13] investigated the role of intramural UFs in infertility by using magnetic resonance imaging (MRI). They have reported a higher frequency of uterine peristalsis during the implantation phase of the menstrual cycle in women with intramural UFs. It could explain infertility in women with this type of UFs [13]. In their later study, same authors showed that myomectomy normalizes the frequency of uterine peristalsis in patients with intramural UFs, exhibiting abnormal findings before myomectomy, thus increasing PR after myomectomy [14].

It is considered that UF could modulate endometrial vascularity and, in that way, affect *in vitro* fertilization (IVF) outcome. Kamel *et al.* [15] investigated the effect of intramural UFs on uterine and endometrial vascularity in infertile patients scheduled for IVF. They reported significantly increased vascularity in the endometrium of the women with UF, as denoted by higher endometrial vascularity index (VI) flow index (FI) and endometrial vascularization flow index (VFI). Also, there was not significant difference in mean uterine artery resistance index (RI) or pulsatilty index (PI). When compared with the control group (non-UF), women with UFs >4 cm had significantly higher endometrial VI, FI and VFI, whereas women with UF ≤4 cm had no statistically significant differences in VI, FI, and VFI. These findings indicated that intramural UFs >4 cm significantly increase endometrial vascularity and that increase in blood flow could be a factor that affects the outcome of IVF.

Sagi-Dain *et al.* [16] analyzed the endometrial thickness and grade measurements in women underwent IVF cycle. Patients with UFs had a decreased endometrial thickness, lower rates of Grade A and higher rates of Grade C endometrium. It has been observed significantly higher spontaneous MR in group of women with UFs, which could be explained by the adverse sonographic appearance of the endometrium. The relationship between uterine fibroids and fertility outcomes.

The relationship between fertility and UFs includes several open questions: influence of UFs on implantation rates (IR) and MR, effects of myomectomy on fertility concerning myometrial healing and subsequent pregnancy complications and the complications due to UFs during pregnancy.

Since the worldwide trend of delayed childbearing is in advanced reproductive age, when infertility is a health issue "per se", all the aspects of UFs and related fertility become particularly important for reproductive medicine specialists. The UFs prevalence, as the only cause of infertility in women, is estimated to be between 1 and 2.4% [12].

5. Implantation rates

The Practice Committee of the American Society for Reproductive Medicine reported that uterine UFs are main cause of infertility in a relatively small proportion of infertile women [17].

Ben-Nagi *et al.* [18] investigated the submucous UFs effect on concentrations of endometrial implantation factors in mid-luteal phase, i.e., glycodelin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNFa) and osteopontin. They reported significantly lower concentrations of glycodelin and IL-10 in such patients. The reduced concentrations of glycodelin in uterine flushing in women with submucous UFs could explain the link between submucous UFs and early pregnancy loss (PL). Knowing that IL-10 is responsible for the protection of the fetus from the potentially harmful maternal immune response, the reduced concentration of IL-10 in of women with submucous UFs, indicate that submucous UFs may harm endometrial receptivity.

Despite a consensus on the detrimental effects of submucous UFs on IR, the interconnection between intramural and subserous UFs and IR remains questionable. The ultrasound view of submucosal uterine fibroid is shown in Fig. 2.

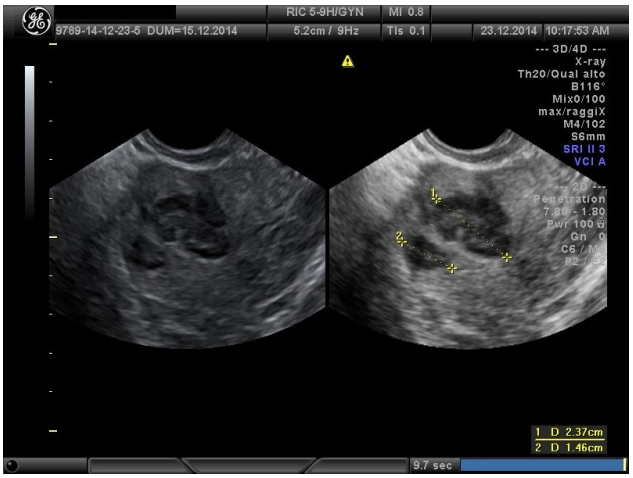

Fig. 2. The ultrasound view of submucosal uterine fibroid. Ultrasound view of submucosal uterine fibroids (1 - submucosal uterine fibroid with diameter of about 2.37 cm; 2 - submucosal uterine fibroid with diameter of about 1.46 cm).

Klatsky *et al.* [19] evaluated IR and PR in cohort of patients undergoing oocyte donor recipient IVF cycles. Ac-

cording to results of these study, both IR and clinical PR were not significantly different between patients with or without UFs. Moreover, clinical PR and IR were not affected by UF localization (subserosal vs intramural), UF number (single vs multiple) and UF size. On the other hand, Sunkara *et al*. [20] conducted a meta-analysis and observed a significant decrease in the live birth and clinical PRs in women with intramural UFs which do not distort the uterine cavity compared with women without UFs.

Yan *et al*. [21] researched the influence of FIGO type 3 UFs (intramural) on *in vitro* fertilization-intracytoplasmic sperm injection (IVF-ICSI) outcomes. They performed a retrospective cohort study which included 151 patients with type 3 UFs and 453 matched control subjects who underwent IVF-ICSI. They observed a significantly lower IR in experimental group. Type 3 UFs also resulted in a lower frequency of live births (LB) rate and clinical pregnancy rate (CPR). The cited author has also reported that patients with type 3 UFs with a single UF diameter (SD) or total reported UF diameter (TD) $>$2.0 cm also had significantly lower rates of LB, CPR and IR. Type 3 UFs with SD or TD $\leq$2.0 cm had no significant influence on IVF-ICSI outcomes.

Oliviera *et al*. [22] have observed that patients with UFs $\leq$40 mm have similar IVF outcomes as those without UFs (IR, PR, and MR). On the other hand, same authors reported that PRs were lower in patients with intramural UFs larger than 40 mm, indicating that at least some of these patients might benefit from myomectomy prior to IVF.

Christopolus *et al*. [23] have evaluated the impact of non-cavity distorting UFs on pregnancy outcomes after IVF. They reported that the presence of non-cavity distorting UFs negatively affects CPR and LB rates in patients undergoing their first IVF/ISCI cycle. It has also been reported significant effect of UFs on LB rate in women with UFs of $>$30 mm in diameter and women with two or more UFs. Also, it has been reported no significant relationship between UFs and pregnancy outcomes in women with single UFs of $<$30 mm in diameter.

Wange *et al*. [24] conducted meta-analysis based on comparative or cohort studies that explored the impact of non-cavity distorting intramural UFs on the efficacy of IVF treatment. They have observed a significant reduction of LB rate, CPR, IR and the significant increase in MR in patients with non-cavity-distorting intramural UFs.

According to results reported by Rikhraj *et al*. [25], patients with non-cavity distorting intramural UFs had 44% lower odds of LB and 32% lower odds of CPR. Subgroup analysis of women with purely intramural UFs showed also significantly lower odds of LB rates and CPR. Subgroup analysis of prospective and retrospective studies showed that non-cavity distorting intramural UFs have a significant detrimental influence on LB rate in women undergoing IVF.

Bai *et al*. [26] conducted a retrospective case control study, targeted to explore the impact of FIGO type 3 UFs on the outcomes after IVF cycles. They compared women submitted to IVF cycle with and without UFs, matched by age, BMI, type and cause of infertility and antral follicle count. The IR, CPR, MR and LB rate were compared between groups. Authors reported that baseline characteristics did not differ between the groups, but women with FIGO type 3 UFs showed significantly lower IR, CPR and LB rate when compared to non-UF controls. No difference was observed in MR. They have also reported that UFs of a maximum diameter $\geq$30 mm or multiple ($\geq$2) UFs decrease the IPR, CPR and LB rate compared with the control group, while the smaller ones or single UF has no impact on IVF outcomes.

There is still debate, whether or not, intramural UFs not distorting uterine cavity could influence fertility and if they should be surgically treated before eventual pregnancy. Many authors reported different cut-off diameters of UFs submitted to surgery for the possible influence on reproductive performance. Usually, myomectomy is performed in case of uterine cavity distorting UFs. Additionally, myomectomy should be considered for UFs without cavity distortion in women with unexplained unsuccessful IVF cycles, after careful evaluation of each case history and weighing the significance of UFs as the main cause of infertility.

The effect of UFs on endometrial receptivity potentially could explain how fibroid influence implantation. The endometrial receptivity, important for implantation of the embryo, is regulated by cytokines, growth factors, hormones and lot of other signaling molecules. The genes HOXA10 and HOXA11 as well as leukemia inhibitory factor are crucial in implantation process. Their expression is decreased in endometrium of women with UFs [27,28]. The bone morphogenic protein-2 (BMP-2) regulate the expression of HOXA10 and HOXA11 genes. It has been reported that UFs secrete transforming growth factor-β3 (TGF-β3), which impairs signaling BMP-2 in the endometrium and it could be implicated in failure of implantation in a fibroid uterus [29]. The accumulation of macrophages and prostaglandin F2-alpha and an inflammatory reaction in endometrium of fibroid uterus could have role in effects of intramural UFs on fertility rate [30].

7. Recurrent pregnancy loss

It has been observed that from 2115 to 60748 miscarriages are linked to UFs annually in the United States in a population aged 25 to 54 years (up to 6.32% of all miscarriages) [1]. There are controversial data in terms of UF localization and size.

Hartmann *et al*. [31] reported that uterine UFs and their characteristics are not associated with risk of miscarriages, concluding that prior evidence attributing miscarriage to UFs was potentially biased. These findings suggest

that surgical treatment of UFs to reduce risk of miscarriage deserves a careful examination. Similar results are showed by Rikraj *et al*. [25], revealing no increase in risk of miscarriage among women with UFs compared with those without.

While the Cochrane database review 2012 stated that there was no evidence of a significant effect of myomectomy on the MR, the Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society of Reproductive Surgeons came to the conclusion – "*In infertile women and those with RPL, myomectomy should be considered only after a thorough evaluation has been completed"* [32]. A recent article stated that all the UFs have detrimental effects on pregnancy: "*Regardless of their siting within the uterus, they reduce the chance of successful implantation of embryos (clinical pregnancy) by 50% and increase the risk of PLs. Within IVF programs the chance of successful LB can therefore be reduced to around 25% of that expected in an age-matched group of women.*" [33].

The clear mechanism which links UF and recurrent pregnancy loss is not still known, but it could be assumed that submucosal and large intramural UF compress the decidua and distort the adjacent vascular architecture interfere with embryo implantation and placentation [34]. The rapid fibroid growth and biochemical factor could predispose abnormal uterine contractility [35].

8. Uterine fibroids and pregnancy

Myomectomy during pregnancy is indicated in very few cases, usually as part of cesarean myomectomy (CM) [4]. The significant question in current reproductive surgery is the relationship between myometrial post-myomectomy scar and pregnancy outcome impairment. Another significant question is the quality of scar is the same if myomectomy was performed by laparotomy, laparoscopy or hysteroscopy and the myomectomy technique itself.

Even though it has been reported that MR are significantly lower after myomectomy, it should not forget the possible risks of development of an abnormally invasive placenta and uterine rupture [24]. There is no consensus between the obstetricians whether the presence of myometrial scar represents an indication for cesarean section (CS) or not [36].

According to large Italian RCT, there were no cases of uterine rupture after abdominal and laparoscopic myomectomies. Authors also didn't find any significant differences when comparing subsequent rates of vaginal deliveries and CSs [37]. Dubuisson *et al*. [36] performed an observational study to investigate the risk of uterine rupture in women who have had laparoscopic myomectomy for at least one intramural or subserosal UF, larger than 20 mm. They reported three cases of spontaneous uterine rupture out of which one occurred on the laparoscopic myomectomy scar, on a total of 145 pregnancies recorded in 98 patients, resulting in 100 deliveries (58 vaginal and 42 CS). Therefore, the risk of uterine rupture after laparoscopic myomectomy was estimated to be 1% (95% CI 0.0–5. 5%). Nevertheless, there is the lack of data which could lead to definitive conclusion on uterine rupture after laparoscopic myomectomy risk, in comparison to abdominal myomectomy [36].

The myomectomy during pregnancy and risk of rupture of uterus after myomectomy, may be interpreted with caution, because it could be influenced by local surgical and obstetric protocols and experienced of gynecologist and obstetrician.

9. Treatments of uterine fibroids and fertility

Currently, there are numerous management options for UFs' treatment. The choice of treatment approach depends on patients' age, attitude towards radical surgery or desire to preserve fertility. Nowadays UF' treatments include hysterectomy/myomectomy performed either by hysteroscopy, laparotomy or laparoscopy, uterine artery embolization (UAE) and magnetic resonance-guided focused ultrasound surgery (MRgFUS) [38].

Hysteroscopic myomectomy is considered as treatment of choice for submucous UF for patients who wants to preserve their fertility [38] and any alternative applied therapy depend on the gynecologist's experience and available equipment [38]. The post-surgery PR, in case of hysteroscopic myomectomy, range from 16.7% to 76.9%, with a mean of 45% [38]. It has been revealed that hysteroscopic myomectomy leads to higher PR than alternative treatments, in women with submucous UFs [11]. On the contrary, Fonge *et al*. [39] showed that, women with submucosal UFs submitted to hysteroscopic removal, have similar birth outcomes to those who do not. The Fig. 3 show recectopic myomectomy.

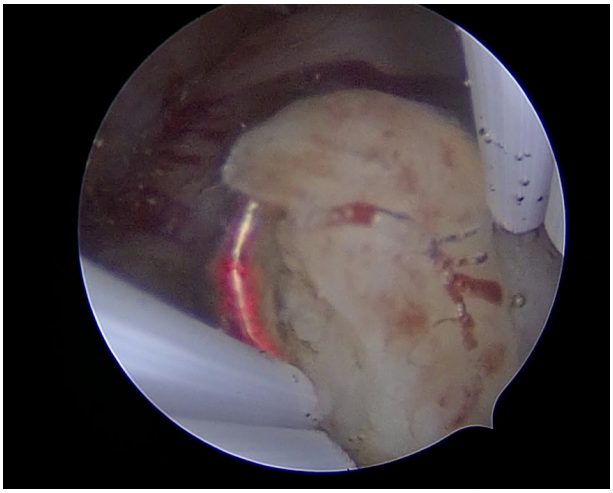

Fig. 3. Resectopic myomectomy.

There are not significant differences in cumulative PR, obstetric or perinatal outcomes when laparoscopic myomectomy is compared to abdominal myomectomy [40].

When fertility preservation is the aim, the medical therapy of uterine UFs is treatment option even though medical treatment does not improve fertility. The negative effect of intramural myoma is related to proximity of uterine cavity and myoma size [41]. Therefore, the medical therapy could be proposed to reduce the size of the uterine myoma. The current medical treatment for uterine fibroid includes oral contraceptives, levonorgestrel-releasing intrauterine system (LNG-IUS Mirena), GnRH agonist (leuprolide, goserelin, triptorelin), selective progesterone receptor modulators. The GnRH antagonist are now in 3 phases of clinical trials [41]. The various options of uterine fibroid medical treatment give a good result in control of uterine fibroids symptoms. The levonorgestrel realizing intrauterine system is dominantly used for control of heavy menstrual bleeding in the absence of fibroids [41]. The disadvantage of this medical treatment is high expulsion rate in case of submucosal fibroids [41]. The levonestrel realizing intrauterine system cannot be used it the uterine cavity is distorted by uterine fibroid. GnRH agonist can be used such as preoperative preparation for reducing uterine and fibroid size and correcting iron deficiency anemia in women with uterine fibroid [41]. Unfortunately, long-term treatment beyond 6 months can reduce bone density and lead to menopausal symptoms [41]. The selective progesterone receptor modulators reduce heavy menstrual bleeding, correct anemia and shrinks fibroids [41]. They do not cause bone demineralization or menopausal symptoms. The using of selective progesterone receptor modulators is associated with endometrial change progesterone receptor modulator-associated endometrial changes and liver injury [41]. Such as other medical treatment options the GnRH antagonist have positive effect on heavy menstrual bleeding, reduce fibroid volume and correct anemia [41]. Even through the GnRH antagonist are in 3 phases of clinical trials, some side-effects are recognized and dose dependent, as well as mineral density loss and menopausal symptoms [41]. There is lack of studies about medical treatment of uterine fibroid and fertility after treatment [41]. The development of the new medical treatment and new therapeutic algorithms for uterine fibroid as well as studies for influence of medical treatment options of uterine fibroid on uterine fibroid related infertility are needed [41].

Uterine artery embolization (UAE), as the treatment option for uterine UFs, did not meet great favor across the globe [42]. Kim *et al*. [43] investigated the effect of UAE on ovarian reserve, based on anti-Mullerian hormone (AMH). They evaluated AMH, antral follicle count (AFC), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) levels, ovarian volume at the 3-month and 12-month follow-up visits at women who underwent UAE. Authors observed no statistically significant differences in serum E2, LH, or FSH levels or ovarian volume 3 or 12 months after UAE. However, AMH and AFC were significantly different 3 and 12 months after UAE. AMH levels remained low after 12 months of follow-up compared to the expected AMH levels. They have observed statistically significant recovery of serum AMH at 12 months compared to at 3 months in <40 years of age women, but not in those ≥ 40 years old. This study showed that ovarian reserve appeared to be affected by UAE in premenopausal women and the younger ovaries (according to biological ovarian age) may have a greater capacity for recovery after ovarian damage [43]. The UAE compared to another method of UF treatment, has the greatest impact on ovarian function [44]. It should be avoided in women with UF seeking fertility improvement [38]. On the contrary Shamy *et al*. [45] have observed that UAE did not have effect on ovarian reserve.

MRgFUS is a combination of thermal ablation of UF using MRI to visualize the UFs. The MRgFUS lead to the higher risk of re intervention than UAE; nevertheless, an absolute decrease in AMH levels at 24 months after the intervention was greater in patients submitted to UAE [46].

Uterine artery occlusion (UAO) during laparoscopy or abdominal myomectomy has no advantages over vaginal occlusion [38]. Sanders *et al*. [47] observed in a meta-analysis that there is not significant difference in CPR and LB rates between women with UAO during myomectomy and women with myomectomy alone.

Interventional ultrasonography is effective method for diagnosing and management of uterine UF. The interventional ultrasonography has no influence on ovarian reserve and AMH levels [48]. Anyway, the choice of treatment depends on the patient's personal treatment goals, as well as its efficacy and the need for repeated interventions.

10. Potential molecular pathways which linked uterine fibroids and infertility

Endocannabinoids and anandamide represent a group of bioactive lipids which have a crucial signal in human reproduction, as potential biomarkers of reproductive impairments [49]. The balance changing between the degradation and synthesis of endocannabinoids lead to local changes in the female reproductive tracts [49]. Also, it has been reported that some components of the endocannabinoid system such as cannabinoid receptors 1, the G protein-coupled receptor GPR55, fatty acid amide hydrolase and N-palmityolethanaolamine are modulated in uterine UFs [50].

Neohormones are molecular group with paracrine or endocrine activity with important roles in physiological functions. One class of the neohormones are relaxin like peptide hormones, which define basic reproductive physiology, such as viviparity with placentation or implantation, lactation and adaptations, required by sperm cells for successful internal fertilization. These roles candidate relaxin like peptides for highly useful biomarkers in characterizing

and monitoring reproductive diseases. H2-relaxin assists in implantation and the development of the placenta in the ovary, whereas its levels change in cases of early miscarriage [49]. Suzuki *et al*. [51] have reported that recombinant H2-relaxin have role in cell proliferation of UFs. Vitamin D, a molecule with numerous roles in human physiology, is a potential marker for reduced fertility and many adverse pregnancy outcome [52]. Numerous epidemiological studies worldwide marked lower levels of vitamin D, as risk factor for uterine UF onset [53,54].

It is well known that thyroid hormones have crucial role in the proper functioning of the female reproductive system, because they modulate the development and metabolism of ovarian, uterine and placental tissues. Therefore, changes in levels of thyroid hormones may result in sub fertility or infertility in women as well as animals [55]. On the other hand, the recent results reported by Saisai *et al*. [56] pay attention on the association between the uterine fibroid and thyroid nodules and thyroid hormones. They have found that the prevalence of thyroid nodules in women with uterine fibroids is significantly higher than that in women without uterine fibroids [56]. They have also observed that women with thyroid nodules have higher proportion of multiple uterine fibroids than women without thyroid nodules [56]. Saisai *et al.* [56] have reported that women with uterine fibroids have lower total triiodothyronine levels than unaffected controls.

The above-mentioned molecules showed a role in uterine UF development, but also in reproductive physiology. Further researches are needed to explain how these molecular pathways link UFs, with infertility and adverse pregnancy outcome.

11. Discussion

In this review, we have showed the complex interplay between UFs and infertility and pregnancy. The clear mechanism which links UF with infertility and pregnancy outcome is still questioned. In the general obstetric population, there are inconsistent results about influence of uterine fibroid on fertility as well as pregnancy outcome. However, for better understanding, the future studies must include women with uterine fibroid diagnosed prior pregnancy and according FIGO subclassification system. Furthermore, the unique system of diagnostic and classification of UF with an emphasis on number, location and type used by experienced gynecologist is important. The classification of patients and taking into account the clinical characteristic which could bias the final results is crucial in future investigations. The new knowledge about influence of uterine fibroid on pregnancy outcome and management of UF during pregnancy requires the better understanding of their differentiation, growth and modification in pregnancy is needed. The animal model and *in vitro* model of cell culture and models of human tissues could give data about molecular and physical changes of UF during pregnancy. The results obtained from *in vivo* and *in vitro* studies explored to human population could be way to the future prevention of unwanted pregnancy outcomes in women with UF.

The pre and post myomectomy studies may provide information about changes in expression of molecules included in endometrial receptivity. The evaluation of impact of new drugs and interventions for uterine fibroid on endometrial receptivity should be necessary for evaluation and regulatory approval.

12. Conclusions

The complete role and true mechanism of UFs influencing fertility is not fully known. There is a lack of quality studies which could give strong information on the link between infertility and UFs. Many information about relationship between UFs and infertility come from speculative studies and, some of these, report that PR after IVF significantly increase when UFs are submucosal. These data about improving PR after myomectomy, lead us to believe that fertility is influenced by UFs. In all of those cases, we have no control groups of women who did not undergo myomectomy. So, the question is: do UFs influence fertility? The future investigations should focus on the molecular mechanisms of infertility, such as genetic basis of UFs development, to develop the best way of medical and surgical management of UFs tailored for each patient, with a better reproductive outcome.

Author contributions

RS, LN, AD, RA, ZM and AT designed the research study. RS, AT, JŠ and ĐT analyzed the data. RS, MA and AT wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no competing interests.

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