Fibroids (myomas) are the most common tumors of the female reproductive organs, consisting of smooth muscle cells, fibroblasts and extracellular matrix. They develop from menarche to menopause. They are diagnosed in 10-20% women of reproductive age. Their size varies from barely visible nodules to large tumors. Change in the size of fibroids during pregnancy and after childbirth is the subject of numerous studies. Most studies indicate a significant increase in the size of fibroids during the first trimester, unchanged size during the second and the third trimester and a decrease in their size after the delivery. The effect of fibroids on pregnancy depends on their number, location and size. Myomas are associated with numerous perinatal complications: bleeding in pregnancy, miscarriages, pain due to red degeneration, preterm birth, placental abruption, placenta previa, intrauterine growth restriction, fetal malpresentation, prolonged labor, increased cesarean section rate, uterine atony and postpartum hemorrhage.

Treatment of fibroids in pregnancy includes bed rest and follow-up with symptomatic therapy in case of pain, as well as intensive monitoring of the fetus. Very rarely, myomectomy may be necessary during pregnancy. Myomectomy during caesarean section has been considered contraindicated for years. Recent research demonstrates that this procedure may not be associated with an increased risk of perioperative complications. Its advantages include performing two operations within one surgical procedure, while avoiding the risks of repeated laparotomy and anesthesia.

The most common postpartum complications of fibroids are bleeding and infection.

**Keywords:** fibroids, pregnancy, perinatal complications, myomectomy.
UVOD

Miomi (fibromi ili leiomiomi) predstavljaju najčešće tumor ženskih reproduktivnih organa [1,2]. Sastoje se od glagotkih mišićnih čelija, fibroblasta i ekstracelularnog matriksa [3]. Obilna količina ekstracelularnog matriksa, koju grade glikozaminoglikani i gusto zbijeni intersticijumski kolagen, čini tkivo mioma dva do četiri puta čvršćim od miometrijuma [4]. Ovi tumori su jasno ograničeni, okruglasti, tvrdi, sivobeli - povećanju koncentracije pojedinih faktora rasta [8]. Efekti na ekspresiju gena povezani sa citokinima i rastom. Njegov uticaj na razvoj ovih tumora ogleda se u gesteron dominantnom faktoru u stimulaciji njihovog celularnog matriksa [9].

Miomi se razvijaju od menarhe do menopauze i utiču na reproduktivno zdravlje tokom većeg dela života žene. Njihovo praćenje i lečenje uzrokuje značajne masu, nasleđe, polne hormone, životne navike (alkohol, ruke, fizička aktivnost, stres), uticaj životne sredine, kao i uticaj hroničnih bolesti, poput hipertenzije [1].

Epidemiološki faktori rizika za nastanak i razvoj mioma uključuju: godine starosti, rasu, indeks telesne mase, nasleđe, polne hormone, životne navike (alcohol and caffeine consumption), diet rich in red meat and soy, smoking, physical activity, stress), uticaj životne sredine, kao i uticaj hroničnih bolesti, poput hipertenzije [3].

Uprkos činjenici da su miomi veoma česti tumori, njihova etiopatogeneza je nedovoljno proučena [8]. Transformacija miometrijalne čelije materice u čeliju mioma sposobnu za klonalnu ekspanziju je inicijalni korak u formiranju mioma. Drugi korak u nastanku tumora je produkcija i akumulacija extracelularnog matriksa [9].

Samo sam rast mioma zavisi od steroidnih hormona. Progesteron je dominantan faktor u stimulaciji njihovog rasta. Njegov uticaj na razvoj ovih tumora ogleda se u efektima na ekspresiju gena povezanih sa citokinima i povećanjima koncentracije pojedinih faktora rasta [8].

BIOLOŠKO PONAŠANJE MIOMA TOKOM TRUDNOĆE

Miomi su jasno ograničeni, okruglasti, tvrdi, sivobeli - časti tumori, čija veličina varira od makroskopski jedva...
vidljivih nodusa do masivnih tumora, koji mogu ispuniti malu karlicu [9]. Promena veličine mioma tokom trudnoće i nakon porođaja je predmet brojnih istraživanja [7,10,11]. Li i saradnici [11] navode da 60 - 78% mioma ne pokazuje značajne promene zapremine tokom trudnoće, a slažu se da se veličina mioma smanjuje nakon porođaja, kao posledica remodeliranja uvećane materice tokom puerperijsuma.

Rosati i saradnici [10] su pokazali da se zapremina mioma uvećava tokom prvog trimestra trudnoće, ostaje nepromenjena tokom drugog i trećeg, a smanjuje se tokom puerperijsuma.

Vitagliano i saradnici [12] su obavili analizu ukučno 12 studija koje su istraživale uticaj trudnoće na veličinu mioma. Trend porasta veličine mioma tokom prvog trimestra je pokazan u svim ispitivanim studijama, dok su podaci o promenama veličine mioma u literaturi tokom drugog i trećeg trimestra neusaglašeni.

U studiji koju su objavili Loflin i saradnici [13], pokazano je značajno smanjenje veličine submukoznih mioma u odnosu na intramuralske, subserozne i miome na peteljci, kao i smanjenje veličine mioma nakon porođaja u odnosu na prvi trimestar trudnoće.

Delli Karpini i saradnici [14] su u svom istraživanju uočili značajan porast veličine mioma u ranoj trudnoći u odnosu na veličinu pre trudnoće, nepromenjenu veličinu mioma tokom drugih polovine trudnoće i značajno smanjenje veličine mioma nakon porođaja.

MEHANIZMI NASTANKA PERINATALNIH KOMPLIKACIJA

Oko 10 - 40% žena sa miomima materice imaju miomima uzrokovane komplikacije tokom trudnoće [11,15]. Uticaj mioma na trudnoću umnogome zavisi od njihovog broja, lokalizacije i veličine. Miomi utiču na rastezanje materice; dovode do promena u strukturi endometrija i obliku materične šupljine; utiču na efikasnost kontrakcija materice tokom porođaja i u puerperijsumu; a mogu predstavljati i prepreku normalnom toku porođaja (tzv. miomi previja) [6,16]. Submukoznii miomi sa sekundarnim degenerativnim promenama mogu predstavljati zarišteto infekcije i/ili hronične inflamacije. Citokini koji se stvaraju u ovim miomima doprinose distensioni materice, što uzrokuje povišenu vrednost oksitocine, što potom doprinosi nastanku prevremenih porođaja [15]. Takođe, miomi mogu ograničiti pokrete ploda tokom trudnoće [6].

BIOLOGICAL BEHAVIOR OF MYOMAS DURING PREGNANCY

Myomas are well defined, round, hard, grey-white tumors, whose size varies from macroscopically barely visible nodes to massive tumors, which may occupy the entire lesser pelvis [9]. Myoma size during pregnancy and after delivery has been the subject of numerous studies [7,10,11]. Lee et al. [11] state that 60 - 78% of myomas do not show significant changes in volume during pregnancy and they agree that the size of myomas decreases after delivery, as the result of the remodeling of the enlarged uterus during the puerperium.

Rosati et al. [10] have shown that myoma volume increases during the first trimester of pregnancy, remains the same during the second and the third trimester, and decreases during the puerperium.

Vitagliano et al. [12] have performed an analysis of a total of 12 studies examining the impact of pregnancy on myoma size. The trend of myoma size increase during the first trimester of pregnancy has been reported in all of the analyzed studies, while the data on the changes in myoma size during the second and the third trimester is not consistent.

A study published by Laughlin et al. [13] has reported a significant decrease in the size of submucosal myomas in comparison to intramural, subserosal, and pedunculated myomas, as well as a decrease in the size of myomas after delivery, as compared to the first trimester of pregnancy.

In their study, Delli Carpini et al. [14] observed a significant increase in myoma size in early pregnancy, as compared to the size prior to pregnancy, unchanged myoma size during the second half of the pregnancy, and a significant decrease in myoma size after delivery.

MECHANISMS OF THE DEVELOPMENT OF PERINATAL COMPLICATIONS

Around 10 - 40% of women with uterine fibroids have myoma-induced complications during pregnancy [11,15]. The effect of myomas on pregnancy largely depends on their number, localization, and size. Fibroids affect uterine distension; they lead to changes in the structure of the endometrium and in the shape of the uterine cavity; they affect the efficiency of uterine contractions during delivery and the puerperium; and can also impede the normal course of delivery (so called myoma previa) [6,16]. Submucosal myomas with secondary degenerative changes may be a focus of infection and/or chronic inflammation. Cytokines produced in these myomas contribute to increased risk of premature delivery. The distortion of the uterine cavity may have a compression effect and lead to disruption in the utero-
KOMPLIKACIJE MIOMA TOKOM TRUDNOĆE I PORODAJA

Miomi u trudnoći se povezuju sa nastankom brojnih perinatalnih komplikacija, kao što su: kravarenje u trudnoći, spontani pobačaji, bol usled crvene degeneracije, intruterini zastoj u rastu ploda, karična prezentacija, kosi i poprečni položaj ploda, prevremeni porodaj, prevremena preterminska ruptura plodovih ovojaka, abrupcija placentae, placenta previa, zastoj porodaja, povećana učestalost carskih rezova i operativnih vagnalnih porodaja, atonija materice, postpartalna hemo-raggija i ruptura materice [6,11,16,17].

Rizik nastanka kravarenja u ranoj trudnoći određen je lokalizacijom mioma i značajno je povećan u slučaju insercije posteljice u blizini mioma [11].

Učestalost spontanih pobačaja je povećana dva do tri puta kod trudnica sa miomima. Rani spontani pobačaji su češći kod žena sa miomima tela materice i u slučajevima implantacije na mestu submukoznih mio-ma. Smatra se da miomi dovede do pobačaja svojim kompresivnim efektom, povećanjem kontraktilnosti materice i komprimovanjem snabdevanja krvlju posteljice i ploda [11,18].

Veliki i multipli miomi povećavaju rizik za nastanak prevremenog porodaja, jer su manje rastežljivi od zdravog miometrijuma, što dovodi do prevremenih kontrakcija materice i dilatacije grlica [18].

Podaci o preterminskoj rupturi plodovih ovojaka kod trudnica sa miomima su neusaglašeni: od toga da je rizik smanjen, preko neizmenjenog rizika do povećanog rizika u odnosu na opštu populaciju. Autori koji su istraživali ovaj problem navode učestalost od 7% [19].

Najčešća komplikacija mioma u trudnoći je pojava lokalizovanog bola u abdomenu, kao posledica crvene degeneracije mioma. Klinički se opisuje kao bol u predelu mioma ili opšta bolna osjetljivost posle palpacije, sa povišenom telesnom temperaturom, leukocitozom, mukom i povraćanjem. Smatra se da brzi rast mioma tokom trudnoće rezultira nedovoljnom snabdevenošću tkiva krvlju, sa posledičnom tkivnom anoksijom i pojavom bola. Drugi uzrok bola mogu biti promene arhitektonike krvnih sudova, uzrokovane uvećanjem gra-vidne materice, što takođe dovodi do tkivne anoksije i nekroze. Treći mogući uzrok može biti lokalno oslobađanje prostaglandina iz nekrotičnih čelija mioma [6,11].

Smatra se da je pojava intruterinog zastaja u rastu ploda češća u trudnoćama u kojima je insercija placente na mestu postojanja mioma materice, što može uzrokovati poremećaj perfuzije placente [20].

Malprezentacija ploda sreće se u 13% trudnoća komplikovanih miomima. Češće se javlja u slučajevi velikih, submukoznih, multiplih i mioma lokalizovanih u predelu donjeg materičnog segmenta [11]. Najčešća je placental circulation. In women with myomas, the activity of the enzyme oxytocinase is reduced, which causes elevated oxytocin levels, which, in turn, contributes to the occurrence of premature deliveries [15]. Also, myomas may limit fetal movement during pregnancy [6].

MYOMA COMPLICATIONS DURING PREGNANCY AND DELIVERY

Fibroids in pregnancy are associated with the development of numerous perinatal complications, such as: bleeding in pregnancy, miscarriages, pain due to red degeneration, intruterine growth restriction, breech presentation of the fetus, transverse and oblique position of the fetus, preterm birth, preterm premature rupture of fetal membranes, placental abruption, placenta previa, prolonged labor, increased cesarean section rate and increased rate of operative vaginal deliveries, uterine atony, postpartum hemorrhage, and rupture of the uterus [6,11,16,17].

Risk of hemorrhage in early pregnancy is determined by myoma localization and is significantly increased in case of placental insertion in the vicinity of the myoma [11].

The frequency of miscarriages is two to three times higher in women who have fibroids. Early miscarriages are more frequent in women with myomas of the body of the uterus and in cases of implantation at the site of submucosal myomas. It is believed that myomas cause miscarriage with their compression effect, with their influence on the increase in the contractility of the uterus, and by compromising blood supply to the placenta and the fetus [11,18].

Large and multiple myomas increase the risk of premature delivery, as they are less flexible than the healthy endometrium. This leads to premature contractions of the uterus and premature dilatation of the cervix [18].

Data on preterm rupture of the fetal membranes in pregnant women who have myomas are not consistent. They range from data demonstrating that the risk is decreased, to data demonstrating no change in the level of risk, to data showing an increased risk, as compared to the general population. Authors who have researched this issue have reported a 7% rate of occurrence [19].

The most frequent complication of myomas in pregnancy is localized pain in the abdomen, which is the result of red degeneration of the myomas. Clinically, it is described as pain in the region of the myomas or general painful sensitivity upon palpation, accompanied by elevated body temperature, leukocytosis, nausea and vomiting. It is believed that the rapid growth of the myomas during pregnancy results in inadequate blood supply to the tissue, resulting in tissue anoxia and pain. Another cause of pain may be found
karlična prezentacija, mada miomi mogu dovesti i do kosog i poprečnog položaja ploda [18].

Abrupcija posteljice je retka, ali potencijalno fatalna komplikacija trudnoće. Rizik za njen nastanak je trostruko povećan kod žena sa miomima. Faktori rizika su submukozni i retroplacentni miomi, kao i miomi za preminu veće od 200 cm³. Jedan od mogućih mehanizama nastanka abrupcije jeste smanjen protok krvi do mioma i okolnog tkiva miometrijuma, što rezultira delimičnom ishemijom i nekrozom decidue u tkivu posteljice koje prekriva miom [11].

Smatra se da je placenta previja dva puta češća kod žena sa miomima. Kao faktor rizika navode se prečnik mioma veći od 50 mm i miomi lokalizovani u predelu donjeg materičnog segmenta [11,18,21].

Faktori koji doprinose većoj učestalosti carskih rezova kod trudnica sa miomima su malprezentacija, distocija i opstrukcija porođajnog kanala miomima u predelu donjeg materičnog segmenta. Rizik se povećava proporcionalno veličini i zapremini mioma, a veći je kod oboljelih između mioma donjeg materičnog segmenta [11,18,19]. Prospektivna kohortna studija iz Sjedinjenih Američkih Država je pokazala da je povećani rizik porođaja carskim rezom kod žena sa pojedinačnim miomima proporcionalan veličini mioma, a kod žena sa multipilim miomima ukupnoj zapremini mioma [22].

Factors contributing to a higher frequency of cesarean sections in pregnant women with myomas are fetal malpresentation, dystocia and obstruction of the birth canal by myomas in the region of the lower uterine segment. The risk increases proportionately to the size and volume of the myoma, and is greater in cases of myomas in the lower uterine segment [11,18,19]. A prospective cohort study from the United States of America showed that the increased risk of cesarean section delivery in women with individual myomas was proportionate to the size of the myoma, and in women with multiple myomas this increased risk was proportionate to the total volume of the myomas [22].

The frequency of the occurrence of postpartum hemorrhage is around 2.5%. This is why postpartum hysterectomy in these women is more common than in the general population (Slika 1) [11]. Multiple myomas, large myomas, and myomas localized in the region of the lower uterine segment increase the risk of hemorrhage [23].
Jedna od najtežih komplikacija tokom trudnoće i porođaja je ruptura materice. Ona može dovesti do krvarenja, šoka, histerektomije, pa čak i smrti majke i ploda [24]. Većinom se dešava u trećem trimestru trudnoće ili tokom porođaja, kada je intrauteriner pritisak povišen. Ožiljci na materici, od prethodne miomektomije, uzrokuju smanjenje elastičnosti i čvrstine miometa. Uzrokom materičkih ožiljaca je zamišavanje mišićnog tkiva fibroznom. Porodac se u ovakvim slučajevima po pravilu završava carskim rezom [11,24].

**THE EFFECT OF MYOMAS ON THE FETUS**

Podaci o uticaju mioma na nastanak intrauterinog za-stoja u rastu ploda su oprečni. Najčešći uzrok morbidi-teta novorođenčadi je zamišavanje miometa sa miomima iz prethodne miomektomije. U svojoj studiji, Saut i saradnici [21] navode da je intrauterina smrt ploda dva puta češća u trudnoćama komplikovanim miomima. Lai i saradnici [16] su pokazali veću učestalost prevremenih porođaja kod trudnica sa miomima u odnosu na one bez mioma, u svim gestacionim starostiima (kako pre 37. nedelje gestacije, tako i pre 34., 32. i 28. nedelje gestacije).

**TREATMENT OF MYOMAS IN PREGNANCY AND DURING DELIVERY**

Treatment of myomas in pregnancy includes bed rest and follow-up with symptomatic therapy in case of pain, as well as intensive monitoring of the fetus [6,11]. Treatment of pain caused by red degeneration of myomas is conservative and includes analgesics, rehydration, and bed rest [11].

In case of the prolapse of myomas into the vagina, myomectomy is not advised, as it can lead to uncontrollable hemorrhage, rupture of fetal membranes, and miscarriage, i.e., premature delivery. Heavy bleeding, intense pain, urine retention, and infection are indications for vaginal resection of the prolapsed myomas during pregnancy [26].

The decision on myectomy during pregnancy is made on the basis of the gestational age of the pregnancy, failure of conservative treatment, the anatomy of the myoma(s), and the existence of degenerative and/or inflammatory changes [27]. The age and the reproductive anamnesis of the patient should also be taken into account [6]. Results are more favorable if myectomy is carried out in the first or second trimester of the pregnancy, especially in the case of myomas

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Miomi do not pose contraindications for vaginal delivery, even in the case of large myomas (diameter greater than 50 mm) [11,26]. In cases of vaginal delivery, they can be the cause of massive postpartum hemorrhage, due to a reduced contractility of the uterus, uncoordinated contractions of the uterus, and possible retention of placental fragments. In some cases, such a situation may be resolved with abdominal myomectomy, with the preservation of the uterus [28].

Myomectomy during cesarean section is considered to be a procedure which could be linked to a high risk of the development of intraoperative and immediate postoperative complications [6]. Lately, more and more studies have shown that myomectomy during cesarean section does not have to be linked to a higher risk of perioperative complications [29].

Myomectomy during cesarean section enables the performing of two operations within one surgical procedure, while avoiding the risks of repeated laparotomy and anesthesia. Significant factors in reaching a decision on this procedure are, in addition to anatomical localization and the number and size of the myomas, also the surgical experience of the obstetrician and the existence of secondary degeneration of the myomas (Figure 2). It is possible to safely remove pedunculated myomas and subserous myomas, whereas enucleation of intramural and multiple myomas during cesarean section is not recommended. An absolute contraindication for myomectomy during cesarean section is uterine hypotonia and/or uterine atony [29].

**MYOMA COMPLICATIONS IN THE PUERPERIUM**

Postpartum infections are more common in women with uterine myoma. It is believed that myomas may be the cause of placental residue after delivery or puerperal sepsis [6]. Prolonged febrile state in the postpartum period in patients with myomas may sometimes be caused by necrotic submucosal myoma contamination. Rarely, spontaneous expulsion of myomas into the vagina may occur during the puerperium [16].

The development of pyomyomas is a rare complication and it usually occurs after delivery or miscarriage, due to myoma infarction or infection. The predisposing factors for the development of pyomyomas include gynecological operations, vascular insufficiency, and immunodeficiency. Infection usually spreads per...
duženo febrilno stanje u postpartalnom periodu kod pacijentkinja sa miomima nekada može da bude prouzrokovano kontaminacijom nekrotičnih submukoznih mioma. Retko, u puerperijumu može doći do spontane ekspulzije mioma u vaginu [16].

Pojava piomioima je retka komplikacija i nastaje obično posle porođaja ili pobačaja usled infarkcije ili infekcije mioma. Predisponirajući faktori za njegov nastanak obuhvataju ginekološke operacije, vaskularnu insuficijenciju i imunodeficijenciju. Infekcija se obično širi per continuitatem iz materične šupljine, ali može na stati i hematogenim i limfogenim putem. Piomioimi se manifestuju visokom temperaturom, mada se u nekim slučajevima može javiti i jak bol u abdomenu. Leče se surgicale metode.

ZAKLJUČAK

Imajući u vidu tehnološki napredak u rezoluciji ultrazvučnih aparata, kao i trend odlaganja rađanja, može se očekivati povećanje prevalencije mioma u trudnoći. Ovo predstavlja značajan izazov za ginekologe i akušere u kontekstu unapređenja reproduktivnog zdravlja žena i sprečavanja eventualnog nastanka komplikacija koje miomi mogu izazvati u trudnoći, tokom porođaja i u puerperijumu.

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