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REVIEW

# Uterine fibroid size modifications during pregnancy and puerperium: evidence from the first systematic review of literature

**Amerigo Vitagliano[1] · Marco Noventa[1] · Attilio Di Spiezio Sardo[2] · Gabriele Saccone[2] · Salvatore Gizzo[1] · Shara Borgato[1] · Salvatore Giovannni Vitale[3] · Antonio Simone Laganà[3] · Giovanni Battista Nardelli[1] · Pietro Salvatore Litta[1] · Carlo Saccardi[1]**

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## Abstract

**Purpose** The influence of pregnancy on uterine fibroid size still remains an unsolved dilemma. Basing on current knowledge, physicians are not able to inform patients about the likelihood of uterine fibroids to modify their size during pregnancy. Study aim was to summarize available evidence concerning the size modifications of uterine fibroids during each trimester of pregnancy and during puerperium.

**Methods** The review was reported following the PRISMA guidelines and registered in PROSPERO (registration number: CRD42017071117). A literature search was conducted in electronic database (PubMed, Embase, Sciencedirect, the Cochrane library and Clinicaltrials.gov) until July 2017. All studies evaluating fibroids' changes during pregnancy and puerperium by ultrasound or magnetic-resonance-imaging were included. Descriptive characteristics of studies and patients were collected. The modifications of uterine fibroid diameter and volume were the outcome measures.

**Results** Concerning the first trimester of pregnancy, all authors reported a significant growth of uterine fibroids. Contradictory evidence was found about uterine fibroid modifications during the second and third trimesters, mainly supporting a slowdown during mid pregnancy and a subsequent size reduction during late pregnancy. Concerning the overall modifications during pregnancy and puerperium, poor evidence quality suggests that uterine fibroids do not modify their volume/slightly enlarge during pregnancy and subsequently reduce in size during puerperium.

**Conclusions** Uterine fibroids seem to be subject to a non-linear trend of modifications during pregnancy and puerperium, which may vary from myoma to myoma. Adequate evidence supports uterine fibroid systematic enlargement during the first trimester of pregnancy, while inconsistent evidence is available about the changes of uterine fibroids during second and third trimesters. In addition, the overall modifications of myomas during pregnancy and puerperium remain unclear.

**Keywords** Uterine fibroids · Fibroid size · Size modifications · Pregnancy · Puerperium

## Introduction

Uterine fibroids (UFs), also known as myomas or leiomyomas, are benign monoclonal neoplasms of the smooth muscle layer of uterus [1, 2]; they represent the most common benign gynecological tumors in young women, with a prevalence increasing with age from 40 to 60% at 35 years to 70–80% at 50 years old [3].

Despite their benign histological features, UFs have considerable economic and social impacts, being the most common clinical indication to hysterectomy in USA and representing a possible cause of hospitalization and complications during pregnancy [2, 4, 5]. As a matter of fact, UFs affect up to 10.7% of pregnant women and in 10–30% of cases may be

✉ Amerigo Vitagliano
amerigovitagliano.md@gmail.com

[1] Unit of Gynecology and Obstetrics, Department of Women and Children's Health, University of Padua, Via Giustiniani 3, 35128 Padua, Italy

[2] Department of Public Health, School of Medicine, University of Naples Federico II, 80131 Naples, Italy

[3] Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood ''G. Barresi'', University of Messina, 98125 Messina, Italy

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responsible of major adverse outcomes, mainly when large [5, 6]. Obstetric complications related to UFs include early and late miscarriage, preterm birth, fetal malpresentation, placental abruption, post-partum hemorrhage, and higher risk of cesarean delivery [6, 7]. Moreover, principally during the early pregnancy, UFs may cause bulky symptoms or severe abdominal pain due to myoma degeneration or torsion, especially in case of pedunculated UF. In selected situations, when leiomyomal cell necrosis and peritoneal reaction occur, performing an urgent myomectomy may be the unique therapeutic option for pelvic pain unresponsive to analgesia [5, 8].

The influence of pregnancy on UFs size is debated for up to 3 decades and still remains an unsolved dilemma: whilst some authors concluded that these neoplasms are likely to be subject to significant increase of size during gestation; other authors state that their volume remains unchanged or even decreased during the course of pregnancy [9–11].

The objective of our systematic review is to analyze all the available evidences about the changes of UFs' size during pregnancy.

## Materials and methods

### Study design

This is a systematic review of the size modifications of UFs during each trimester of pregnancy and during puerperium.

The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

### Study registration

The systematic review was registered in PROSPERO before to start the literature search (registration number: CRD42017071117).

### Inclusion criteria

- *Population*: Pregnant women with UFs as diagnosed by ultrasound (US) and/or magnetic-resonance imaging (MRI).
- *Intervention*: Two or more following measurements of UFs.
- *Comparator*: None.
- *Timing*: From pre-gestational age to puerperium.
- *Outcomes*: Assessment of UFs' size modifications at each stage of pregnancy and after birth.
- *Study designs*: Observational studies (prospective, retrospective, and non-concurrent cohort studies, case–control studies, case series). We will include both full reports and data from conference abstracts describing observational studies.
- *Language*: Only studies reported in English language.

### Search strategy

A systematic literature search was conducted in electronic database (PubMed, Embase, Sciencedirect, the Cochrane library, and Clinicaltrials.gov) until July 2017 without date restriction.

The search used specific key words and database indexing terminology. The key search terms included: uterine fibroids OR uterine myomas OR uterine leiomyomas modification OR enlargement OR reduction (Mesh/Emtree) AND pregnancy OR first trimester of pregnancy OR second trimester of pregnancy OR third trimester of pregnancy OR puerperium.

### Study selection and data extraction

Two authors (A.V. and M.N.) independently screened titles and abstracts of studies obtained by the search strategy. The text of each potentially relevant study was obtained and assessed for inclusion in each section of the review, independently by the two authors. A manual search of reference lists of retrieved studies and available review articles was successively performed to avoid missing relevant publications. The same authors (A.V. and M.N.) also independently extracted data from studies about study features (design, setting, objectives, and main findings), population characteristics (age, ethnicity, inclusion criteria, and gestational age at recruitment), UFs measures (diameter and volume), and timing of UFs' measurements. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. One other author (C.S.) independently reviewed the selection and data extraction process. The results were compared, and any disagreement discussed and resolved by consensus.

According to the different endpoints of our study (reported below), each manuscript was systematically evaluated for inclusion in each section of our review on the basis of the time interval in which UFs modifications were investigated (first trimester, second trimester, third trimester, puerperium, and entire pregnancy).

### Endpoints of the systematic review

We settled five endpoints according to the precise period of pregnancy in which UFs modifications were evaluated: modifications of UFs during the first trimester of pregnancy;

modifications of UFs during the second trimester of pregnancy; modifications of UFs during the third trimester of pregnancy; modifications of UFs during the puerperium; overall modifications of UFs induced by pregnancy.

### Data synthesis and analysis

We reported all descriptive characteristics of study including study design, year of publication, study setting, type and number of patients, and size and number of UFs evaluated. The modifications of UFs diameter (cm) and volume ($cm^3$) were the measures of effect for this systematic review.

Since there was a marked heterogeneity among studies in the timing of UFs measurement and outcome measures reported, a quantitative data synthesis was not performed.

### Risk of bias

The methodological quality of each study was independently assessed by two authors (A.V. and M.N.) with Quality Assessment Tool for Before–After (Pre–Post) Studies with No Control Group (available at https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after) that considers 12 "yes/no" items and gives one point for each affirmative answer. This quality assessment tool was used to estimate the ability of each study to draw associative conclusions about the effects of exposure (specific timeframes of pregnancy and puerperium) on outcome (size modifications of UFs). Studies were considered with poor, fair, and good quality rating, respectively, if scoring less than 4 points, between 4 and 7 points, and at least 8 points. Disagreements between reviewers were resolved through discussion and adjudication of a third reviewer (C.S.).

## Results

### Study selection

The literature search based on our pre-defined key search item identified 3233 publications, after removing duplicates. The titles of these manuscripts were screened, resulting in 86 studies considered potentially eligible to be included in the review. Of the total of relevant manuscripts identified, 70 studies were excluded after the examination of the abstracts and 16 studies were further evaluated. After the evaluation of full text, four studies were additionally excluded: two manuscripts were review articles [8, 13]; one study assessed exclusively the prevalence of UFs in pregnancy without evaluating their modifications [10]; one additional study [14] potentially reported duplication of data included in another study [15]. Finally, we identified nine full-text manuscripts [9, 10, 15–21] and three congress abstract [22–24] eligible for this systematic review after applying our inclusion and exclusion criteria (see Fig. 1).

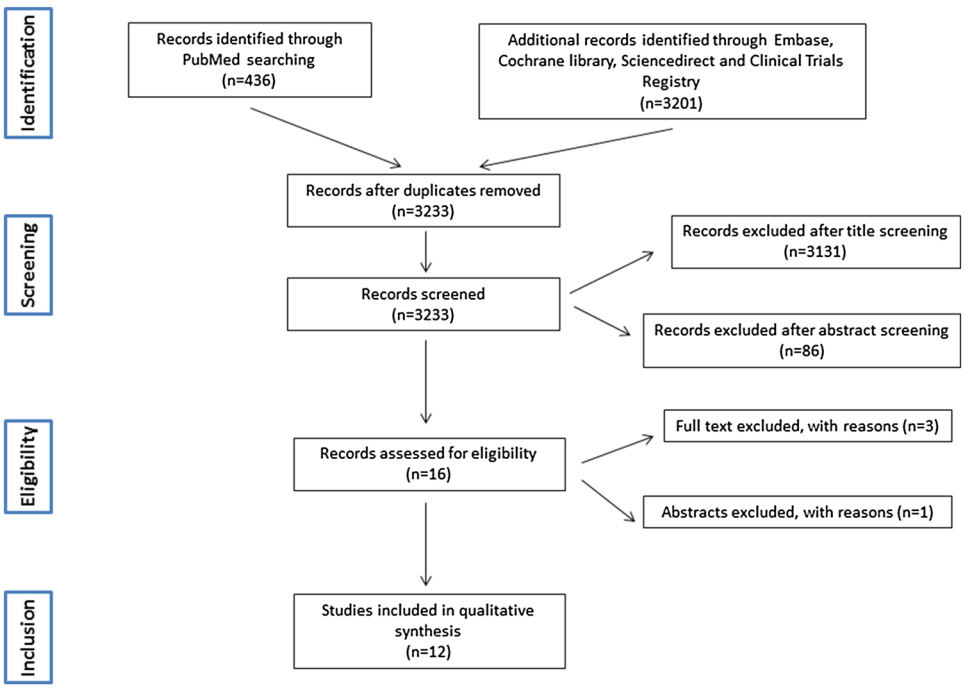


**Fig. 1** PRISMA flow diagram

## Included studies

Twelve studies with a total of 807 participants were included in this systematic review. Seven were prospective cohort studies [9, 10, 15, 17, 19, 23, 24], one was a prospective controlled study [16], three were retrospective studies [18, 20, 21], and one was a case series [22]. In all studies, the measurements of UFs were performed with US, except for Laughlin et al. [10] who used MRI exclusively to confirm UFs modifications (previously evaluated by US) during puerperium. All general characteristics of studies are summarized in Table 1.

### Type of patients

*Ethnicity*: Two studies evaluated only white women [9, 19]. Two additional studies included mainly white women (respectively, 89.1% in Muram et al. [20] and 62% in Laughlin et al. study [10]. Lev-Toaff et al. [17] and Hammoud et al. [18] evaluated mainly black women (respectively, 79.6 and 89.4%). The remaining studies did not provide data about ethnicity [15, 16, 21–24].

*Parity*: Patients were mainly nulliparous in five studies (respectively, 87.2% [9], 78.9% [18], 64% [16], 61% [21], and 57.1% [19]). In one study, half were nulliparous and half pluriparous [10], while in the remaining studies, parity was not reported [15, 17, 20, 22–24].

### Type of fibroids

*Minimum size evaluated*: Three studies [15, 20, 21] analyzed only UFs with mean diameter greater than 30 mm. Three other studies [9, 16, 19] evaluated all UFs with mean diameter greater than 10 mm (< 50 mm in diameter in Benaglia et al. [16] and Ciavattini et al. [9] studies). Other studies did not report clear data about the minimum mean UFs diameter evaluated [10, 17, 18, 22–24].

*Position*: UFs were mainly located in corpus uteri in all studies [9, 10, 17, 19–21] providing data, especially in anterior wall (51.2 and 66% in Winer-Muram [21] and De Vivo studies [19]), mainly in posterior wall (55.2%) in Ciavattini et al. study [9]. Remaining studies did not report data [15, 16, 18, 22–24].

*UFs subtype*: Intramural and subserosal were the main UFs evaluated in the two studies [9, 19] reporting clear data (90.5% intramural and 9.5% subserosal in De Vivo et al. study [19]; 50% intramural and 50% subserosal in Ciavattini et al. study [9]). In addition, Laughlin et al. [10] evaluated the correlations between UFs subtype and their modifications (without providing data about the number of UFs subtypes evaluated). The majority of the authors [15–18, 20–24] did not provide data.

## Modifications of uterine fibroids

According to variety of information provided by the authors, five studies [10, 16, 20, 22, 23] were included exclusively in one section, three studies in two sections [9, 21, 24], three studies in three sections [17–19], and one study in five sections [15].

Main findings and qualitative modifications of UFs are reported in Table 2 and illustrated in Fig. 2.

### First trimester of pregnancy

Four studies [9, 15–17] evaluated UFs modifications during the first trimester of pregnancy. In the majority of studies [9, 15, 16], patients received the first UFs measurement before conception (1 month before IVF cycle [16], within 4 months [9] or 1 year [15] before conception), except for Lev-Toaff et al. [17] study, in which timing of UFs measurements was not reported. Ciavattini et al. [9] performed US twice at 7–8 and 10–13 gestational weeks (GW), Rosati et al. [15] every 2–4 weeks during the whole first trimester, while Lev-Toaff et al. [17] and Benaglia et al. [16] only once during the first trimester.

In all studies, a trend of growth of UFs was found. In Benaglia et al.'s experience [16], a significant increase in mean diameter (+ 34%; from 17 ± 10 to 23 ± 13 mm, $p < 0.001$) and median volume of UFs was reported (+140%; from 1.6 mL [0.5–5.5] to 5.2 mL [1.4–14.7]) in the initial pregnancy (until 6–7 GW), involving all UFs independently from their initial size [16]. Similarly, a significant growth in median diameter and median volume was reported by Ciavattini et al. [9] at 7–8 GW US (respectively, from 18 mm [12–25] to 25 mm [18–30] and from 3.1 $cm^3$ [0.9–8.2] to 8.2 $cm^3$ [3–14.1]; $p < 0.01$), with a further increase at the second US evaluation at 10–13 GW (up to 31 mm [27–40] in diameter and to 15.6 [10.3–33.5] in volume, $p < 0.01$). In agreement with other authors [9, 16], Rosati et al. [15] reported a significant increase in UFs volume during the first trimester (+ 8.21% in comparison to pre-pregnancy volume), as well as Lev-Toaff et al. [17] observed a mean increase in UFs diameter during such period, even if not significant (probably due to small sample size evaluated: 17 UFs).

### Second trimester of pregnancy

UFs modifications during such period were investigated by five studies [9, 15, 17–19]. In the majority of studies [9, 15, 18, 19], timing of UFs' measurement was clearly described, except in Lev-Toaff et al. paper [17].

**Table 1** General features of the studies

| Study ID | Study design | Country | Patients (number) | Age (years) | Ethnicity | Fibroids (number) | Fibroids (initial size) | Time at recruitment | US scans (number) | Timing of US evaluations (GW) |
|---|---|---|---|---|---|---|---|---|---|---|
| Muram et al. (1980) | Retrospective | Canada | 41 | 31 (CI 24–41) | Mainly caucasian (89.1%) | 41 | D 3–5 cm ($n = 16$)<br>D 5–10 cm ($n = 20$)<br>D > 10 cm ($n = 5$) | nr | nr | nr |
| Winer-Muram et al. (1983) | Retrospective | Canada | 89 | nr | nr | 89 | D 3–5 cm ($n = 37$)<br>D 5–10 cm ($n = 43$)<br>D > 10 cm ($n = 9$) | 10–20 GW | ≥ 3 | 28 GW (all patients); others variable |
| Lev-Toaff et al. (1987) | Prospective | USA | 71 | CI 20–49 | Mainly black (79.6%) | 162 | D 2–5.9 cm ($n = 111$)<br>D 6–11.9 cm ($n = 51$) | nr | > 2 | nr |
| Aharoni et al. (1988)[a] | Prospective | Israel | 29 | nr | nr | 32 | nr | 4.4 GW (CI 3–6) | nr | Every 3–8 weeks until puerperium |
| Rosati et al. (1992) | Prospective | Italy | 36 | CI 24–41 | nr | 36 | nr | Before pregnancy or at 9–12 GW | nr | Every 2–4 weeks during the whole pregnancy and puerperium |
| Neiger et al. (2006)[a] | Prospective | USA | 72 | nr | nr | 137 | nr | 14.4 GW (SD ± 5.4) | 3.7 ± 2.1 (mean ± SD) | nr |
| Hammoud et al. (2006) | Retrospective | USA | 107 | 31 (± 6) | Mainly black (89.4%) | nr | nr | 16–19 GW | ≥ 2 | 16–19, 20–30, 31–42 |
| Ozturk et al. (2009)[a] | Case series | Turkey | 19 | nr | nr | 37 | nr | nr | nr | nr |
| Laughlin et al. (2010) | Prospective | USA | 171 | 31.2 (± 4.8) | Mainly white (62%) | 171 | D 1.9 cm (0.4–8 CI) | 8 GW (CI 7–10) | 2 | Early pregnancy; puerperium |
| De Vivo et al. (2011) | Prospective | Italy | 38 | 33.9 (± 5.1) | Caucasian | 42 | D 1.1 cm (0.76–1.48) | 11–14 GW | 3 | 11–14; 20–22; 32–34 |
| Benaglia et al. (2014) | Prospective controlled | Italy | 25 | 36.7 (± 3.4) | nr (IVF) | 46 | D 1.7 cm (± 1) | One month before IVF cycle | 2 | 6–7 |
| Ciavattini et al. (2016) | Prospective | Italy | 109 | 34.7 (± 4.8) | White | 143 | D 1.8 cm [1, 2, 5]<br>V 3,1 $cm^3$ (0.9–8.2) | During the year before pregnancy | 4 | 7–8; 10–13; 20–22 |

Data concerning patients' age are expressed in mean (± SD) or median (with CI 95%)

*GW* gestational weeks, *SD* standard deviation, *CI* confidence interval, *nr* not reported, *D* diameter, *V* volume

[a]Study in abstract form

**Table 2** Main findings of the included studies

| Study ID | Main findings |
|---|---|
| Muram et al. (1980) | In 38/41 myomas, no change in size during pregnancy was observed. In two cases, diameter increased of 20 and 25%, whilst in one patient, a reduction of 20% in diameter was found[b] |
| Winer-Muram et al. (1983) | In 82/89 of the patients, there was no change in the size of myoma from the first ultrasound to pregnancy term; in 6, there was an increase in size (by up to 4 cm in diameter); and in 1 case, the neoplasm decreased in diameter by 2 cm. All the 31 patients available for rescanning 6-week post-partum showed a marked decrease in the size of the myomas[b] |
| Lev-Toaff et al. (1987) | During the first trimester, regardless of original size, myomas enlarged ($n = 17$). During second trimester, the fashion was dependent to original size of lesions (small myomas: 30.3% increased and 14.5% decreased; large myomas 48.3% decreased and 13.8% increased). During the third trimester, a general size reduction was found (34.8% of small myomas and 58.8% of large myomas)[b] |
| Aharoni et al. (1988)[a] | No increase in size during the pregnancy was observed in 25 fibroids (78%). Only 7 (22%) increased in size but by no more than 25% of the initial volume. At 6-week post-partum, the size of the fibroids did not differ significantly from the size during pregnancy[c] |
| Rosati et al. (1992) | A general increase in myoma size during the first trimester of pregnancy (especially before 10th week of gestation) and no evident enlargement during the remainder of the pregnancy were found, with a subsequent reduction in size during puerperium. No correlations between growth of myoma and their original size were observed[d] |
| Neiger et al. (2006)[a] | On average, there was no significant change in the size of leiomyomas during pregnancy. Size of myomas varied significantly during pregnancy[b] |
| Hammoud et al. (2006) | In the second trimester, 55.1% of myomas decreased in size (mean decrease in volume of 35%), while 44.9% of myomas enlarged (mean increase in volume of 69%). In the third trimester, the 75% became smaller (mean decrease in volume of 30%), while 25% enlarged (mean increase in volume of 102%). Mean diameter of 4 cm or more was highly predictive of size reduction during third trimester |
| Ozturk et al. (2009)[a] | No enlargement of myomas was observed during pregnancy[c] |
| Laughlin et al. (2010) | 79% of myomas resulted smaller in puerperium in comparison to first measurement. Median diameter was subject to a median change of 0.5 cm. Submucous fibroid reduction (1.8 cm change) was higher than intramural (0.2 cm), subserous (0.6 cm), or pedunculated (0.5 cm) fibroids. Fibroids in the lower segment were associated with a greater change in fibroid diameter (1.4 cm) when compared to fibroids in the corpus (0.5 cm) or fundus (0.4 cm)[b] |
| De Vivo et al. (2011) | 71.4% of uterine myomas grew between the first and second ultrasound and 28.6% remained unchanged or became smaller; the percentage of enlargement was slightly lower (66.6%) between the second and third investigations. Volumetric increase correlated negatively with multiparity and maternal age, respectively, between first and second scan and the first and third scan[d] |
| Benaglia et al. (2014) | A statistically significant increase of myoma size emerged in the pregnant group, with a median increase of diameter of all the lesions of + 34%, whilst the median volume increase was + 140%[b,d] |
| Ciavattini et al. (2016) | A volume increase of 122% was observed during the interval of the first to the second ultrasound, whereas a median growth of 108% was detected during the interval between the second and the third ultrasound and of 25% between the third and the fourth ultrasound. Smaller fibroids grew more frequently in comparison with larger ones A significant positive correlation between hCG levels and diameter of myomas between 5 and 12 weeks emerged[b,d] |

[a]Study in abstract form

[b]Evaluated with average diameter modifications

[c]Outcome measure not reported

[d]Modifications expressed in volume modifications

De Vivo et al. [19] observed a significant increase of mean UFs volume between the first (11.6 ± 0.5 GW) and second US scan (20.6 ± 0.4 GW), from 17.04 ± 29.1 $cm^3$ at the first scan to 38.8 ± 67.8 $cm^3$ at the second scan ($p = 0.006$). Similarly, Ciavattini et al. [9] reported a significant increase of UFs size between 10 and 13 and 20 and 22 GW (from 15.6 $cm^3$ [10.3–33.5] to 24.4 $cm^3$ [10.3–35.1], $p < 0.01$), even if lower in comparison to UFs enlargement during the first trimester (mean increase + 2.6 vs + 8.5 $cm^3$ during the first trimester).

Differently, in two other studies [17, 18], a variable pattern of growth of UFs was reported. In particular, Hammoud et al. [18] observed that almost half of UFs reduced in size (55.1%) and half increased in size (44.9%) in the interval between 16 and 19 and 20 and 30 GW, with a pooled median reduction of UFs volume (from 56.38 to 45.08 $cm^3$, $p = 0.001$). In addition, Lev-Toaff et al. [17] observed two different trends of size changes according to the initial fibroid size: among small fibroids (< 6 cm mean diameter), the 30.3% increased in size, and the 14.5% decreased in size, while in the group of large fibroids (≥ 6 cm mean diameter), the 13.8% increased in size and 48.3% decreased in size (quantitative data not provided). Finally, Rosati et al. [15] reported a slight increase of UFs

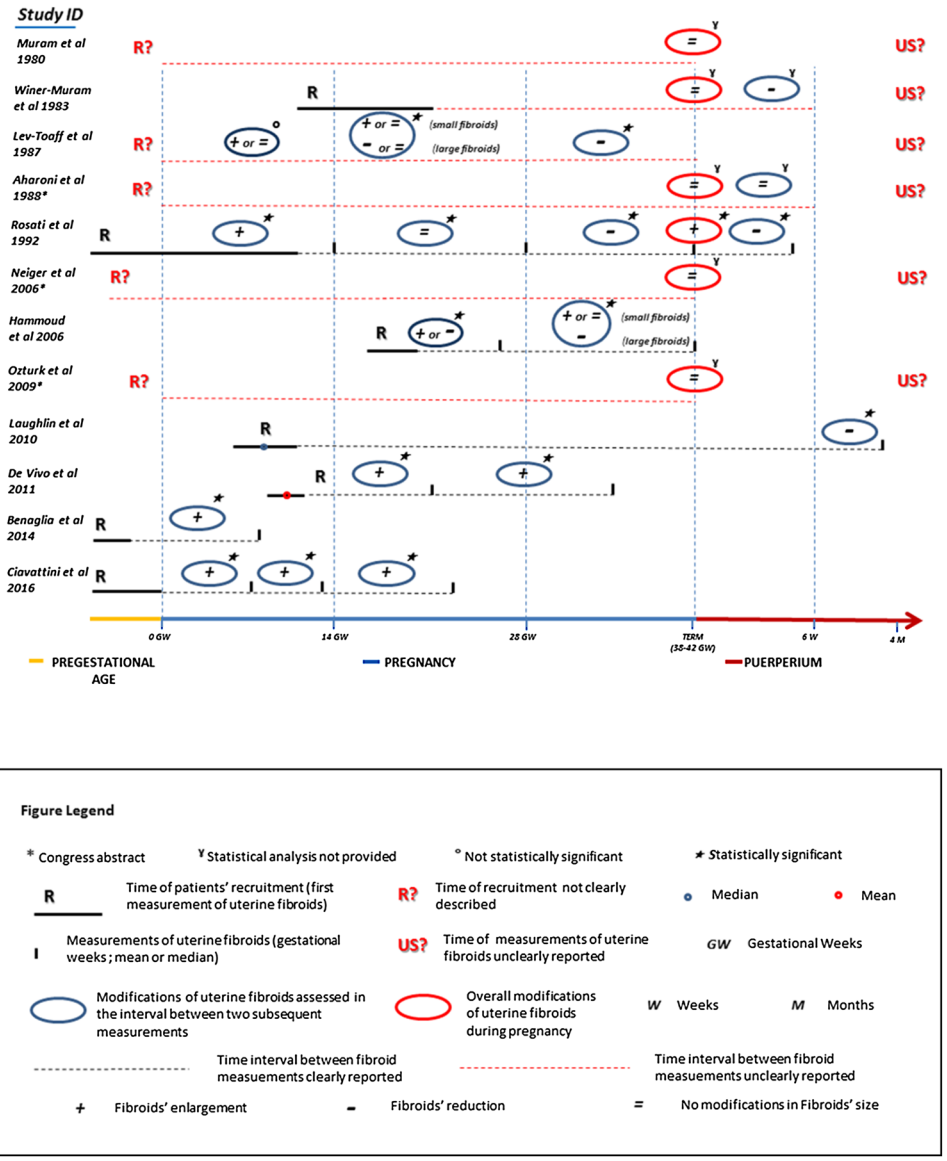


**Fig. 2** Illustrative picture of main findings of the systematic review

volume between 14 and 27 GW (+ 4.65%), which was not statistically significant.

### Third trimester of pregnancy

Four studies investigated the modifications of UFs during the third trimester of pregnancy [15, 17–19]. Timing of UFs' measurement was clearly described in three studies [15, 18, 19].

In detail, Rosati et al. [15] observed a mean reduction in UFs volume of − 0.51% (± 4.16). Differently, Hammoud et al. [18] observed a pooled increase of UFs volume (from 45.08 to 52.87 $cm^3$), but the percentage of UFs enlarging was about 20% (mean increase in volume of 102%), with the majority of UFs (75%) reducing in size (about − 30% in pooled volume). Moreover, a major tendency to decrease in volume was observed in large UFs (88.1% of UFs with diameter > 4 cm), while small UFs (< 4 cm in diameter) mainly increased in size or showed no modifications (40% increased, 40% no change, and 20% decreased).

In the other hand, Lev-Toaff et al. [17] reported a main trend of reduction in size during the third trimester especially for large UFs (≥ 6 cm mean diameter), with 58.8% of lesions reducing in size (and remaining lesions showing no change). In addition, 34.8% of small UFs (< 6 cm mean diameter) reduced in size, and remaining UFs showed no change. Data about pooled modifications in size of UFs were not provided by Lev-Toaff et al. [17].

Finally, De Vivo et al. [19] reported a volumetric increase for 66.6% of UFs (between 20.6 and 33.1 GW), with a volume growth rate per week of 2%; such increase was slightly lower in comparison to the second trimester (between 11.6

and 20.6 GW; 71.4% of UFs increase; 7.4% growth rate per week), but, however, significant ($p = 0.03$). No data about pooled volume/diameter were reported.

#### Overall modifications during pregnancy

Seven studies evaluated the modifications of UFs size during the entire course of pregnancy [10, 15, 20–24]. The timing of UFs measurements was inadequate/unclear in the majority of studies [20–24], except in two studies [10, 15]. In Winer-Muram et al.'s study [21], the first US examination was performed between 10 and 20 GW, and Laughlin et al. [10] evaluated UFs enlargement from 6 to 7 GW to postpartum, whilst in three additional studies [20, 22, 24], the time of the first UFs measurement was not clearly reported. Only Rosati et al. [15] and Neiger et al. [23] (data from meeting abstract) compared the final size of UFs with pregestational size.

Rosati et al. [15] observed a significant mean increase of UFs' volume from pre-gestational age to the end of pregnancy (11.85% ± 6.45), with a subsequent return to original size during puerperium, whilst Neiger et al. [23] reported no significant change in UFs size during the entire course of pregnancy. In Winer-Muram et al. study [21], there was no demonstrable change in the size of UFs in 82 patients (among 89 patients), while in 6 patients, there was an increase in size (by up to 4 cm in diameter), and in 1 patient, UF decreased by 2 cm in diameter. Similarly, Muram et al. [20] observed no modifications of UFs in 38 of 41 patients evaluated, whilst in the remaining three patients, a reduction (− 20%) of UFs diameter or an increase of UFs (+ 20 and + 25% in diameter) was found. Accordingly, Ozturk et al. [22] reported no enlargement of UFs during pregnancy, as well as Aharoni et al. [24] mainly observed no size changes in the majority of UFs (78%) systematically measured, with only 7 UFs (22%) increasing in size (but by no more than 25% of the initial volume).

Finally, Laughlin et al. [10] reported that 79% of Ufs resulted smaller in puerperium in comparison to first measurement (performed at 8 GW), with greater reduction of submucous UFs in comparison to intramural and subserous UFs.

#### Puerperium

Only three studies published before 2000 [15, 21, 24] evaluated the modifications of UFs size during puerperium. Clear data about the timing of UFs measurement were provided only by Rosati et al. [15], reporting a consistent reduction of UFs size during puerperium (− 12.87% ± 28.12 in mean volume). Winer-Muram et al. [21] observed a decrease in UFs diameter of at least 50% in all patients ($n = 31$) available for rescanning 6-week post-partum (quantitative data about UFs size not reported). Differently, Aharoni et al. [24] reported that 6 weeks after delivery the size of the fibroids did not differ significantly from the size during pregnancy (data from meeting abstract).

### Assessment of the risk of study BIAS

All studies published exclusively in abstract form were considered at high risk of bias [22–24] (poor quality judgement). Two additional studies of old publication date [20, 21] were judged as qualitatively insufficient due to lack of study objectives explanation, absence of clear inclusion criteria for patients' enrollment, small sample size, and absence of inferential statistical analysis.

Five studies were considered as qualitatively fair [15–18]; however, concerns about their risk of bias were raised by the absence of clear inclusion criteria for patients' enrollment in Rosati et al.'s study [15], the small sample size in three studies [15–17], the unclear/inconsistently delivery of UFs measurement across the study population in two studies [17, 18], high percentage of loss to follow up (38,43%) in Laughlin et al.'s study [10], and single assessment of UFs measures in four studies [10, 16–18].

Finally, two studies [9, 19] were considered at low risk of BIAS (good quality judgement), even if their results are potentially affected by single measurement of UFs size and by the small number of patients evaluated in De Vivo et al.'s experience [19]. Data are shown in Tables 3 and 4.

Given the low number of studies included in each section, publication bias was not assessed.

## Discussion

In line with the current trend of delaying childbearing, the frequency of pregnant women affected by UFs is significantly increasing [9]. Although up to 70% of pregnancies conclude without complication, in the remaining situations, UFs may be responsible of a multitude of obstetrics problems, potentially occurring during each trimester of gestation [2, 4].

According to different authors, the risk of UF-related complications during pregnancy might be primarily correlated with the size of lesions, while the exact localization of tumors (submucosal, intramural, or subserosal) may be responsible for different, specific kinds of adverse events [8, 25, 26]. Anyhow, UFs may be frequently subject to significant volumetric modifications during gestation. It complicates the clinical management of patients affected by UFs [1, 13, 27]. Moreover, basing on the current knowledge, physicians are not able to inform patients about the real likelihood of UFs to persist, regress, or

**Table 3** Quality assessment of the studies according to "Quality Assessment Tool for Before–After (Pre–Post) Studies with no Control Group"

| Study ID | Muram et al. (1980) | Winer-Muram et al. (1983) | Lev-Toaff et al. (1987) | Aharoni et al. (1988) | Rosati et al. (1992) | Neiger et al. (2006) | Hammoud et al. (2006) | Ozturk et al. (2009) | Laughlin et al. (2010) | Vivo et al. (2011) | Benaglia et al. (2014) | Ciavattini et al. (2016) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1) Was the study objective clearly stated? | NO | NO | YES | NR | YES | NR | YES | NR | YES | YES | YES | YES |
| 2) Were selection criteria for the study population prespecified and clearly described? | NO | NO | YES | NR | NO | NR | YES | NR | YES | YES | YES | YES |
| 3) Were the participants in the study representative of those who would be eligible for the test in the general population of interest? | NR | NR | NR | NR | NR | NR | YES | NR | YES | YES | NO | YES |
| 4) Were all eligible participants that met the prespecified entry criteria enrolled? | NR | NR | YES | NR | NR | NR | YES | NR | NO | YES | YES | YES |
| 5) Was the sample size sufficiently large to provide confidence in the findings? | NO | NO | NO | NR | NO | NR | YES | NR | YES | NO | NO | YES |
| 6) Was the test clearly described and delivered consistently across the study population? | YES | YES | NO | NR | YES | NR | NR | NR | YES | YES | YES | YES |
| 7) Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants? | YES | YES | YES | NR | YES | NR | YES | NR | YES | YES | YES | YES |
| 8) Were the people assessing the outcomes blinded to the participants' exposures? | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 9) Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis? | NA | NA | YES | NR | YES | NR | NA | NR | NO | YES | YES | YES |
| 10) Did the statistical methods examine changes in outcome measures from before to after the exposure? Were statistical tests done that provided p values for the pre-to-post changes? | NO | NO | YES | NR | YES | NR | YES | NR | YES | YES | YES | YES |
| 11) Were outcome measures of interest taken multiple times before the exposure and multiple times after the exposure? | NO | NO | NO | NR | YES | NR | NR | NR | NO | NO | NO | NO |
| 12) Did the statistical analysis take into account the use of individual-level data to determine effects at the group level? | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Quality rating (Good, Fair, or Poor) | POOR | POOR | FAIR | POOR | FAIR | POOR | FAIR | POOR | FAIR | GOOD | FAIR | GOOD |

Poor Fair Good

Quality rating criteria: POOR: < 4 points; FAIR: ≥ 4–8 points; GOOD: > 8 points

*NA* not applicable, *NR* not reported

even increase in volume after the completion of pregnancy, inducing to postpone each clinical consideration after puerperium [6, 16].

## Main findings

In spite of the abundance of scientific manuscripts speculating about diagnosis, medical, and surgical treatment of

**Table 4** Authors' judgement of study quality and fibroids' modifications reported by each single study


UFs [28–31], our review revealed an unexpected paucity of data about the growth pathway of such lesions during pregnancy.

Concerning the first trimester of pregnancy, all authors [9, 15–17] reported a significant growth of UFs. These results are supported by adequate evidence quality (four studies [9, 15–17] with fair/good quality judgement including 218 UFs), suggesting that UFs are likely to grow in the first trimester of gestation. However, the magnitude of UFs enlargement was not quantifiable due to heterogeneity in outcome measures.

Differently, despite the overall evidence quality was fair/good, we found contradictory data about the modifications of UFs during the second trimester of pregnancy. In detail, if two studies [9, 19] found a prevalent growing trend of UFs during such period (even if slower in comparison to the trend reported during the first trimester in Ciavattini et al.'s study [9]), two other studies [17, 18] reported a variable trend of growth of UFs, with approximately half growing and half reducing in size. Finally, Rosati et al. [15] observed no significant change in UFs' volume.

Such inconsistency of findings may be attributable to the heterogeneity of studies in terms of chronological realization (from 1987 to 2016), timing of US examinations and/or study populations, or perhaps may support a non-linear trend of growth of UFs during the second trimester of pregnancy. To further stress the last hypothesis, we noted that the authors reporting a mean increase in UFs size [9, 19] performed US measurements earlier (11.6–20.6 GWs and 10–13 to 20–22 GW, respectively) in comparison with the authors [15, 17, 18] reporting different results (14–27 GWs and 16–19 to 20–30 GWs, respectively). This suggests that UFs may undergo a progressive slowdown during the second trimester [9], up to stabilization and a subsequent regression [17, 18]. In addition, as suggested by two studies [17, 19], some UFs may start to reduce in size earlier (at the beginning of the second trimester) and other significantly later (during the second half of gestation), probably in relation to their initial size (with larger lesions starting to reduce in size earlier in comparison to smaller lesions). Nevertheless, in the absence of consistent evidence, UFs modifications during the second trimester need further clarification.

Similarly, available evidence (supported by studies with fair/good quality) does not allow a clear appreciation of the modifications of UFs during the third trimester. A significant size reduction was reported by two studies [15, 17], while Hammoud et al. [18] observed that UFs mainly reduced in size if larger than 4 cm (in diameter) and enlarged/did not change if smaller than 4 cm (in diameter). Differently, De Vivo et al. [19] found a significant increase in UFs volume in comparison to the previous US evaluation (performed between 11.6 and 20.6 GWs).

As well as for data showed about the second trimester, a chronological difference in UFs measurements was present

among studies. Such difference may hypothetically explain the inconsistency between results provided by De Vivo et al. [19] (first US scan performed earlier, see Fig. 2) and those reported by other authors [15, 17, 18]. However, even if UFs seem to be more likely to reduce their volume during the third trimester, such speculation needs to be clearly confirmed by further studies [8, 18].

Concerning the overall modifications of UFs during pregnancy and puerperium, the quality of available evidence is poor; indeed, the majority of studies were judged at high risk of bias [20–24], except Rosati et al. [15] and Laughlin et al. [10] studies. In addition, some concerns are present about the timing of UFs measurements (unclear of inadequate in the majority of studies [10, 20–24]). In particular, regarding the overall changes of UFs in pregnancy, the majority of the authors reported no modifications [20–24] except Rosati et al. [15], who reported a mean increase in UFs volume in comparison to pre-pregnancy measurement. Differently, regarding the modifications of UFs during puerperium, all studies reported a size reduction [15, 21] or no changes [24]. Therefore, even if available data mainly suggest that UFs do not modify their volume/slightly enlarge during pregnancy and subsequently reduce in size during puerperium, adequate evidence quality is needed to clarify the topic.

### Implications

The hormonal and molecular mechanisms involved in UFs modifications during pregnancy are unclear and will represent a challenging field of research. At this regard, some authors argued that the remarkable growth of UFs during the initial pregnancy could be related to other pregnancy-related hormones rather than sex steroids [19]; indeed, serum concentrations of estrogen and progesterone are conversely higher in the second half of pregnancy [9, 16]. In particular, an exciting hypothesis is the "LH-hCG myomal receptors hyperstimulation" due to serum embryonic-hCG increase in the early gestation; such speculation is supported by a recent clinical study showing a statistical correlation between UFs enlargement (in volume) and exponential growth of hCG during the first trimester of gestation [9]. In addition, in vitro studies found that the exposition of leiomyomal cells to exponentially increasing concentrations of hCG results in dramatic hypertrophic and hyperplastic changes, with a progressive decrease in modifications as the culture period progressed [32–34]. This time-limited stimulating effect of hCG may also insightfully explain the progressive slowdown of UFs observed by different authors during the second trimester [15, 17]. Nevertheless, given the possible histological heterogeneity of UFs in terms of percentages of smooth muscle cells and collagenous matrix, it is possible that the expression of LH receptors may be different from myoma to myoma, leading to a wide range of sensitivity to hCG stimulation [16, 33, 34].

However, besides the interesting hypothesis about hCG-driven UFs growth, a plethora of other hormones, enzymes, and growth factors secreted by the maternal and feto-placental compartments markedly increase during the early pregnancy [35]. We cannot exclude that such molecules may exert a concomitant effect on fibroid growth, as the potential effects of all these substances have not been systematically investigated. Similarly, other factors such as myoma–placental site relationship and UFs location (submucosal, intramural, or subserosal) may somehow influence their growth trend [8, 10, 13, 19].

### Limits

The results of our review are limited by the features of included studies, such as study quality (five of 12 studies judged as qualitatively poor) and design (mainly retrospective), small sample size, lapse of time in study realization (from 1987 to 2016), and different methodology (ultrasound equipment, expertise of sonographers, gestational age at UFs measurements, and racial characteristics of populations). Moreover, a quantitative data synthesis was not performed (due to significant heterogeneity among studies in outcome measures and in timing of UFs measurements), limiting the robustness of our findings. Finally, the assessment of UFs through US, although validated in clinical practice, is exposed to a certain degree of inaccuracy in relation to UFs diagnosis (lacking of histological confirmation) and measurements [9, 16, 18, 36].

## Conclusions

UFs seem to be subject to a non-linear trend of modifications UFs during pregnancy and puerperium, which may vary from myoma to myoma (both in terms of timing and quality of changes). Approximately, fibroids may undergo an intriguing "triphasic trend" of changes during pregnancy, with a first phase of enlargement during the first trimester, an intermediate stage of slowdown and stabilization during the second trimester, and a third phase of volume regression during late pregnancy and puerperium. In particular, adequate evidence supports UFs systematic enlargement during the first trimester of pregnancy. Differently, few data are available about the changes of UFs during second and third trimesters, as well as poor evidence is available about the overall modifications of such tumors during pregnancy and puerperium. Moreover, the impact of UFs characteristics (size, position, and subtype) and patients features (ethnicity and parity) on UFs changes needs to be further investigated [36–38].

Our study provides the first summary of evidence about the modifications of UFs during pregnancy and puerperium, highlighting the existing deficiencies in the literature on this topic. Given the plethora of clinical–pathological implications of UFs growth during pregnancy, the present manuscript will figure as "eye opener" to scientists about the necessity of further research on this topic. Clear evidence is needed to allow a more conscious clinical management, as well as appropriate counseling of pregnant patients suffering from UFs. Adequately powered prospective studies comprising seriated UFs measurements from pre-conceptional period (and during the whole pregnancy) to puerperium are mandatory to clarify the issue.

**Author contributions** AV: conceptualization, data curation, formal analysis, investigation, methodology, and original draft writing. MN: conceptualization, data curation, and investigation. ASS: supervision, validation, and review and editing. GS: validation, original draft writing, and review and editing. SG: supervision, and review and editing. SB: methodology and original draft writing. SGV: validation, visualization, and review and editing. ASL: validation, original draft writing, and review and editing. GBN: supervision, and review and editing. PSL: supervision, validation, and review and editing. CS: conceptualization, project administration, supervision, and review and editing.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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