# Growth trend of small uterine fibroids and human chorionic gonadotropin serum levels in early pregnancy: an observational study

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**Objective:** To analyze the growth trend of small uterine fibroids during early pregnancy, evaluating the potential factors involved, with particular interest in hCG levels.
**Design:** Observational study.
**Setting:** Tertiary care university hospital.
**Patient(s):** Women who had an ultrasound diagnosis of small myomas (diameter, ≥10 mm and ≤50 mm) from January 2007 to December 2013, and who subsequently became pregnant within 1 year.
**Intervention(s):** None.
**Main Outcome Measure(s):** Three additional ultrasound examinations were performed during early pregnancy (7–8, 10–13, and 20–22 complete gestational weeks, respectively) and the modifications in diameter and volume of each uterine fibroid were recorded. A serial evaluation of hCG serum levels from 5–12 weeks was performed.
**Result(s):** From the 109 women who fulfilled the study inclusion/exclusion criteria, a significant increase emerged, both for volume and diameter of the detected fibroids. Specifically, a median growth rate (GR) of 122% was observed during the interval of the first to the second ultrasound, whereas a median GR of 108% was detected during the interval between the second and the third ultrasound, and a median GR of 25% between the third and the fourth ultrasound. A significant positive correlation between hCG levels and diameter ($R = 0.69$) of myomas between 5 and 12 weeks emerged.
**Conclusion(s):** A remarkable nonlinear growth of small fibroids during initial pregnancy was observed, with a faster rate in the first trimester and a slowdown by midpregnancy. Those changes seem to be related to the similar increase of hCG levels until 12 weeks. (Fertil Steril® 2016;105:1255–60. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Myomas, pregnancy, growth, volume, hCG

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Uterine fibroids (also known as myomas or leiomyomas) are the most common benign gynecological tumors. The incidence of uterine fibroids increases with age, varying from 40%–60% at 35 years old to 70%–80% at 50 years old (1), and other factors such as obesity (2) also appear to be involved in the development and growth of these lesions, especially in postmenopausal women.

The prevalence of uterine fibroids among pregnant women ranges from 0.1%–10.7% (3–5), but is probably underestimated because of the limitations of physical examination in pregnant women and because of a lower diagnostic accuracy of sonography during pregnancy. In addition, reflecting the growing trend of delaying childbearing and the increasing rate of obesity, the incidence of fibroids during pregnancy is likely to augment in the coming years.

The current evidence regarding the influence of pregnancy on uterine fibroids is conflicting. Although it is a common belief that fibroid size increases during pregnancy, several studies reported that they frequently remained unchanged or even decreased

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in size (6, 7). More recent studies (8, 9) reported a nonlinear increase in dimensions, with more growth in the first half of pregnancy, particularly during the first trimester.

Several mediators affect the growth of uterine fibroids, and among these, estrogens (Es), P, and possibly other hormones such as hCG play a contributing role. All of these hormones undergo wide fluctuations during the entire course of pregnancy, and could affect the growth of fibroids with different temporal patterns, reflecting the different hormones' serum levels for the specific gestational period.

In particular, the hypothesis of an effect of hCG on fibroid growth is not novel and there are convincing in vitro studies supporting this possibility. The presence of functional LH-hCG receptors on fibroids has been repeatedly demonstrated (10, 11). In addition, functional studies showed that hCG increases fibroid cell number both directly (12) and through an autocrine/paracrine effect mediated by PRL secretion (10, 13).

Considering the increasing incidence of uterine fibroids during pregnancy and the possible correlation between the size of fibroids and adverse obstetric events (14), it is important to obtain accurate information regarding the possibility of growth of such lesions during pregnancy. Even the specific period of pregnancy in which the growth might occur more frequently and the factors affecting these changes should be better understood.

Thus, we conducted an observational study on women who were diagnosed with small uterine fibroids and who achieved a spontaneous pregnancy, monitoring the size and dimensions of myomas during pregnancy, to evaluate the hypothesis of a nonlinear growth pattern. We focused on women with small uterine fibroids (mean diameter, $<5$ cm) and with no more than four fibroids, to better observe any change induced by pregnancy and to avoid potential confounders. As a secondary objective, we tried to identify potential factors associated with the change in size of fibroids, with particular interest to the possible role of hCG.

## MATERIALS AND METHODS

This was an observational study that included all childbearing-age women who were diagnosed with small uterine fibroids at the gynecological ultrasound unit of our institution from January 2007 to December 2013, and who subsequently became pregnant within 1 year from the diagnosis. Women were eligible if they were diagnosed before pregnancy with at least one uterine fibroid with a mean diameter $\geq 10$ mm and $\leq 50$ mm. Additional inclusion criteria were single viable pregnancy and white race. All of the eligible patients signed an appropriate consent, granting their permission (if pregnancy occurred within 1 year) for future serial assessments of hCG serum levels and ultrasound monitoring of fibroids during early pregnancy. These patients underwent routine clinical and sonographic assessments at our center throughout the course of pregnancy.

Exclusion criteria were multiple pregnancies, presence of more than four fibroids, evidence of submucosal fibroids, and suspected adenomyosis. Women were also excluded if they underwent IVF treatments and if they were diagnosed with spontaneous miscarriage or ectopic pregnancy (EP). The local ethical committee's approval was properly obtained for this study. The background characteristics recorded from each patient were age, prepregnancy body mass index (BMI), obstetric history (gravidity, nulliparity, previous spontaneous miscarriage, previous EP), maternal comorbidities (such as hypertension and diabetes), past estroprogestinic therapy, and tobacco use.

All women included in the present study underwent four complete transvaginal ultrasound examinations, performed by a senior sonographer with particular competence in gynecological pathology, with a 3.5- to 5.5-mHz probe and a Voluson 730 pro (GE Healthcare). The first ultrasound was performed at the gynecological ultrasound unit of our institution from January 2007 to December 2013. Women who were diagnosed with at least one uterine fibroid with a mean diameter of $\geq 10$ mm and $\leq 50$ mm, who subsequently became pregnant within 1 year (assuming the last menstrual period as the starting point of pregnancy) and who fulfilled the other inclusion and exclusion criteria were included in the present study. The second scan was performed between 7 and 8 complete gestational weeks, the third scan between 10 and 13 complete gestational weeks, and the fourth scan between 20 and 22 complete gestational weeks. In the second and third scans, obstetric parameters, such as embryonic or fetal viability, gestational sac localization, and crown-rump length, were also recorded (15). In the fourth scan, a complete second trimester morphology ultrasound was performed.

Myomas were sonographically defined as symmetrical, well-defined, hypoechoic, and heterogeneous masses. During each ultrasound, myoma location (intramural or subserous), topographic site (anterior/posterior), and placental relationship (remote or retroplacental) were accurately reported. The exact location of each fibroid was recorded for paired analyses. Three perpendicular diameters (d1, d2, and d3 in millimeters) obtained by the mean of three measurements were collected for each fibroid. The volume (in cubic centimeters) was approximated with the ellipsoid formula: $4/3*\pi*(d1*d2*d3)/8$, as already described by other investigators (8, 9). Changes in myoma volume ($\Delta V$) between two scans were calculated as the difference between the last (LV) and the starting (SV) volume (LV - SV) of each ultrasound. Growth rate (GR; % increase) was defined by the formula: $GR = (100*\Delta V/SV)$, whereas GR (% increase) per week (GRw) was calculated for each myoma using the formula: $GRw = GR/Iw$, where Iw is the interval in weeks between the periods considered (8). We considered the last menstrual period as the starting point of the interval between the first and the second scan.

Fibroids were defined as "increased" when an increase in volume of at least 30% (assumed as clinically relevant) between two scans was reported; otherwise they were classified as "unchanged" in size. A weekly determination of hCG levels was performed in every patient from 5–12 gestational weeks, with an ELISA-based assay (VIDAS, bioMerieux; intra-assay coefficient of variability, 5.2%; interassay coefficient of variability, 5.6%).

Statistical software SPSS 20 (SPSS Inc.) was used for data analysis. All variables were tested for normality with the D'Agostino-Pearson test. Normally distributed variables (age, BMI, and gestational age) were expressed as mean ± SD, whereas skewed variables (volume, diameter, ΔV, GR, and GRw) were reported as median and interquartile range (IQR). Qualitative variables were expressed as proportions. Comparison of myoma volumes was performed with the paired *t* test, with a logarithmic transformation when appropriate. A Pearson's *R* coefficient was determined for correlation between hCG serum level and diameter of fibroids until 12 gestational weeks. A multivariate logistic regression was used to identify possible factors associated with the change in size of fibroids, in particular we tested the association between age, BMI, gravidity, parity, myoma location, topographic site, placental relationship, and SV with respect to the number of "increased" fibroids between two ultrasounds for each study period. A $P<.05$ was considered statistically significant. The approval of the local ethic committee was obtained to collect data.

## RESULTS

Among the 7,138 childbearing-age women who underwent a routine gynecological ultrasound scan at our institution during the study period, 2,596 (36.4%) white women were diagnosed with at least one uterine fibroid with a diameter of ≥10 mm and ≤50 mm. One hundred thirty-three patients (5.1%) subsequently became pregnant within 1 year from diagnosis and were recruited for the study. Twenty-four patients did not satisfy the inclusion criteria and were excluded, in particular 12 women were diagnosed with an early spontaneous miscarriage, 7 had a multiple pregnancy, and 5 underwent IVF treatments. No late spontaneous miscarriage was recorded.

The 109 remaining women constituted the study cohort. The background characteristics of the study population were reported in Table 1. A single myoma was found in 87 (79.8%) patients, whereas 13 patients (11.9%) presented two myomas, 6 patients (5.5%) presented three myomas, and 3 patients (2.8%) presented four myomas. The median (IQR) volume and diameter of the lesions were 3.1 $cm^3$ (0.9–8.2 $cm^3$) and 18 mm (12–25 mm), respectively. Fourteen fibroids (9.8%) were identified as subserous and 129 (90.2%) as intramural. The topographic site was anterior for 54 (37.8%) myomas, posterior for 79 (55.2%), and lateral for 10 (7.0%). Seven (4.9%) fibroids were classified as "retroplacental." The total number of lesions remained constant in each scan. The second ultrasound was performed at a mean gestational age of 7.6 weeks (SD ± 0.6 weeks), whereas the third scan was performed at a mean gestational age of 11.9 weeks (SD ± 0.7 weeks), and the fourth ultrasound was performed at a mean gestational age of 21.1 weeks (SD ± 0.8 weeks). The median diameter and volume of all uterine fibroids in each scan are reported in Table 2.

**TABLE 1**

**Background and clinical characteristics of the study population (n = 109).**

| Characteristic | Data |
|---|---|
| Maternal age (y) | 34.7 ± 4.8 |
| BMI (kg/$m^2$) | 24.6 ± 3.7 |
| Gravidity | 1 (1–2) |
| Nulliparity | 95 (87.2) |
| Previous spontaneous miscarriage | 24 (22) |
| Previous ectopic pregnancy | 1 (0.9) |
| Maternal comorbidities | 6 (5.5) |
| Past estroprogestinic therapy | 17 (15.6) |
| Smoking | 4 (3.7) |

*Note:* Data are mean ± SD, median (IQR), or n (%) as appropriate. BMI = body mass index; IQR = interquartile range.

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A significant increase emerged both for volume and diameter ($P<.001$) among the four ultrasound scans. One hundred fifty-one fibroids had a significant "increase" in volume in at least one of the three study periods. More specifically, 110 (76.9%) fibroids were classified as "increased" in volume in the first period between the two scans, 103 (72%) in the second period, and 58 (40.6%) in the third. Taking into account the interval between first and second scan, median (IQR) ΔV, GR, and GRw were 3.1 $cm^3$ (1.2–7.9 $cm^3$), 122% (38.4%–363%), and 15.8% (5%–47.8%), respectively. A median (IQR) ΔV, GR, and GRw of 8.5 $cm^3$ (0.4–13.2 $cm^3$), 108% (17.6%–277.3%), and 25.2% (4.3%–72.4%), respectively, were observed in the interval between second and third scan. The median (IQR) ΔV, GR, and GRw for the interval between third and fourth scan were 2.6 $cm^3$ (0.3–6.4 $cm^3$), 20.1% (1.9%–35.7%), and 2.1% (0.2%–3.7%), respectively.

By analyzing the possible clinical variables involved in the growth of uterine fibroids, the multivariate logistic regression showed a significant association exclusively with SV. In particular, smaller fibroids seem to grow more and more frequently compared with larger ones, with an odds ratio (OR) of 0.97 (95% confidence interval [CI] 0.95–1.0) ($P=.04$), OR = 0.93 (95% CI 0.89–0.97) ($P<.001$), and OR = 0.95 (95% CI 0.92–0.99) ($P<.001$), respectively, for the three intervals (Table 3).

In the study population, hCG serum levels increased exponentially, from a mean value of 8,295 mUI/mL (SD ± 787 mUI/mL) at 5 gestational weeks to a mean of 237,650 mUI/mL (SD ± 75,670 mUI/mL) at 12 gestational weeks. Figure 1 shows the correlation plot between hCG serum levels and diameter of fibroids during early pregnancy in each patient. In addition, the Pearson's *R* coefficient for the correlation between hCG serum levels and diameter of myomas was 0.69 ($P<.0001$).

## DISCUSSION

Reflecting the current trend of delayed childbearing, the incidence of uterine fibroids during pregnancy is increasing. In addition, a possible correlation between fibroids size and adverse obstetric outcomes emerged in previous published studies (14, 16). For this reason, a better understanding of the possibility of growth of such lesions during pregnancy appears to be of particular clinical relevance.

## TABLE 2

**Volume and diameter of fibroids during the study period.**

| Characteristic | I ultrasound | II ultrasound | III ultrasound | IV ultrasound | *P* value |
|---|---|---|---|---|---|
| Volume ($cm^3$) | 3.1 (0.9–8.2) | 8.2 (3–14.1) | 15.6 (10.3–33.5) | 24.4 (10.3–35.1) | < .001 |
| Diameter (mm) | 18 (12–25) | 25 (18–30) | 31 (27–40) | 36 (27–40.6) | < .001 |

*Note:* Data are median (interquartile range).

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In the present study we observed a significant increase for most of the identified myomas during the first half of pregnancy, but the growth trend did not appear to have a linear correlation with the gestational age. Despite a significant increase in the absolute values of both the median diameter and volume of fibroids during the study period, the GR% showed a deceleration in the ultrasound performed at a more advanced gestational age, in particular beyond the first trimester.

These results appear to be consistent with a recent study by Benaglia et al. (9). Comparing the characteristics of uterine fibroids in 25 women undergoing IVF with 25 controls failing to achieve pregnancy, they reported a rapid and remarkable growth during initial pregnancy.

Furthermore, in our cohort, the significant growth of uterine fibroids in the first half of pregnancy did not seem to be related to the background and clinical variables investigated. In the multivariate analysis, no association was found with maternal age, BMI, gravidity, and parity. Local factors, such as location of uterine fibroids, topographic site, or placental relationship, seem to affect this growth trend. The only variable that presented a significant yet slight negative association with the increase in volume of fibroids was the SV of each period between scans. This result would seem to indicate that smaller lesions increase in size more frequently during pregnancy, but the association is probably too weak to draw solid conclusions. Those findings are in contrast with those of De Vivo et al. (8), who reported that the volumetric change of myomas seems to be influenced by parity and prepregnancy BMI and appears more evident in younger than older pregnant women, regardless of the initial size of fibroids.

The first weeks of pregnancy seem therefore to play an important role in the growth of uterine fibroids and the involved mediators could be identified among those that undergo relevant changes of concentration in this gestational period. Estrogen and P are the best-known growth factors for uterine fibroids, but their concentration-trend in pregnancy is different from the growing trend of fibroids. Those hormones increase progressively during pregnancy, reaching a serum concentration of 120–150 ng/mL in the third trimester from a starting serum concentration of 15–20 ng/mL (17).

The rapid and remarkable growth of uterine fibroids during initial pregnancy could be due to other pregnancy-related hormones than sex steroids, and our findings strengthen this conclusion. This was already pointed out by Benaglia et al. (9).

Considering the many hormones and mediators that undergo a significant increase in early pregnancy, it is particularly difficult to identify the specific growth trigger and probably many substances act in synergy with not yet fully explained mechanisms. The current evidence in literature supports the hypothesis of a possible key role of hCG. The rapid exponential increase of serum hCG in the first weeks of pregnancy may explain the similar rapid growth trend of fibroids. In our cohort, a significant positive correlation between the increase of hCG serum levels and the diameter of uterine fibroids during early pregnancy emerged, as shown in Figure 1. Thus, in a period of pregnancy in which the hCG levels increase significantly, so also the size of the fibroids shows a similar increase. This possibility is supported by in vitro studies demonstrating that functional LH-hCG receptors are present on fibroids (10, 11), that hCG level

## TABLE 3

**Logistic regression of possible factors associated with the increase in volume of uterine fibroids.**

| | I–II ultrasound | | II–III ultrasound | | III–IV ultrasound | |
|---|---|---|---|---|---|---|
| **Variable** | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** |
| Maternal age (y) | 0.99 (0.88–1.11) | .88 | 1.05 (0.93–1.18) | .41 | 1.07 (0.97–1.19) | .18 |
| BMI | 1.07 (0.91–1.26) | .41 | 0.96 (0.84–1.10) | .58 | 1.05 (0.93–1.20) | .43 |
| Gravidity | 1.02 (0.51–2.05) | .96 | 1.37 (0.68–2.75) | .38 | 0.58 (0.29–1.12) | .11 |
| Nulliparity | 1.04 (0.15–7.25) | .97 | 0.46 (0.08–2.66) | .38 | 0.37 (0.06–2.21) | .27 |
| Location | 1.26 (0.72–2.19) | .42 | 1.15 (0.64–2.04) | .64 | 0.90 (0.55–1.47) | .66 |
| Topographic site | 1.44 (0.25–8.22) | .68 | 1.73 (0.24–12.40) | .59 | 1.86 (0.26–13.18) | .53 |
| Retroplacental | 1.05 (0.11–10.0) | .97 | 1.55 (0.16–14.82) | .71 | 8.20 (0.96–69.88) | .06 |
| Starting volume | 0.97 (0.95–1.0) | .04 | 0.93 (0.89–0.97) | < .001 | 0.95 (0.92–0.99) | < .001 |

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio.

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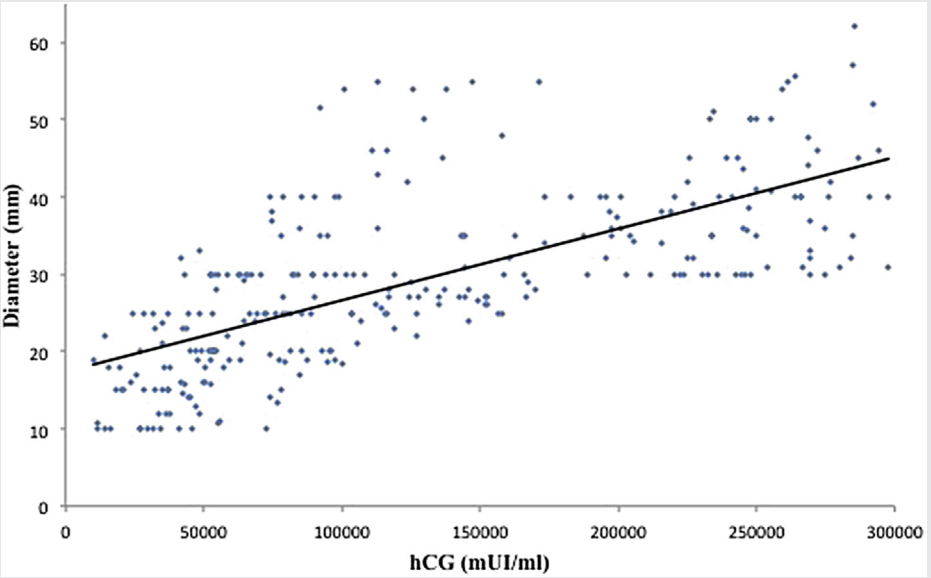
## FIGURE 1




Correlation plot of hCG serum levels and diameter of fibroids. $R = 0.69$; $P<.0001$.

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increases fibroid cell number directly and through PRL as a mediator (10, 13), and that the LH-hCG receptor in myoma cells requires the exponential growth of hCG to maintain its stimulating effect (18).

A potential limitation of our study is the sonographic method of evaluation of fibroids, with the inevitably ultrasound-related degree of imprecision. We tried to overcome this limitation by using a standard technique for fibroids diagnosis and measuring. Uterine fibroids are not perfect spheres, thus volume determination should be approximated, and the ellipsoid formula appear to be the most suitable, as described in previous published studies (8, 9). For these reasons, the exact definition of small fibroids, the calculation of fibroid volume, and the evaluation of volume increase could be affected by an inevitable risk of inaccuracy. All ultrasound examinations were performed by the same senior sonographer and potential unclear cases with large (>50 mm) or multiple fibroids (>4) were excluded. In support of this, the number of lesions coincided in all scans.

Our results are strengthened by the large number of women included, by the early and close monitoring of fibroids characteristics, and by the determination of hGC levels for appropriate comparison. Furthermore, our study population was homogeneous and, to avoid potential confounders, only women with small fibroids (mean diameter, <5 mm) and no more than four fibroids were included. In addition, the dimensional progression of uterine fibroids was well documented during pregnancy in all the women included.

In conclusion, small uterine fibroids seem to grow rapidly in the first weeks of pregnancy, with a nonlinear trend, increasing at a faster rate in the first trimester and undergoing a slow down by midpregnancy. Considering the potential clinical implications of uterine fibroids during pregnancy, and the possible correlation between fibroids size and adverse obstetric events, patients with a prepregnancy diagnosis should be properly informed of the possibility of an increase in size of the lesions. Those rapid volumetric changes are probably related to the similar rapid changes in concentration of hGC in the same gestational period but seem not to be influenced by other clinical factors or characteristics of fibroids.

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