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 ≥ 10 mm and ≤ 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 ≥ 10 mm and ≤ 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 (ΔV) 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%).