Hyperstimulation during IVF cycles does not modify dimensions of small subserosal and intramural leiomyomas

To evaluate the influence of IVF on the dimension of leiomyomas, we selected 72 women with small intramural or subserosal leiomyomas and assessed the size of these lesions before and after the treatment cycle. The mean ± SD diameters of the tumors at these two time points were 20.5 ± 9.5 and 20.6 ± 10.2 mm, respectively, thus supporting the conclusion that IVF does not influence the growth of these lesions. (Fertil Steril® 2011;95:2489–91. ©2011 by American Society for Reproductive Medicine.)

Key Words: Leiomyoma, myoma, fibroid, IVF

There is a general and growing consensus that small nonsubmucosal fibroids should not be removed before initiating an IVF cycle (1–6). Interestingly, a recent study showed that leiomyomas not disturbing the endometrial cavity alter the expression pattern of some endometrial genes but not the genes involved in implantation (7). Nevertheless, some questions remain open. In particular, a neglected but possible concern is the risk of disease progression due to ovarian hyperstimulation for IVF. Indeed, ovarian steroids have a role in the development of leiomyomas (8, 9). In postmenopausal women, hormone replacement therapy has been shown to increase the risk of developing these tumors (10). Because serum E2 concentration rises considerably during an IVF cycle, it cannot thus be excluded that this treatment may contribute to the progression of the disease. To our knowledge, there is no evidence in the literature regarding this.

In the present prospective study, we aimed to estimate the impact of ovarian hyperstimulation for IVF on the dimension of subserosal and intramural leiomyomas. To this aim, patients scheduled for an IVF–intracytoplasmic sperm injection (ICSI) cycle between June 2007 and June 2009 in our Infertility Unit were considered for study entry. Women were eligible if they were diagnosed with asymptomatic subserosal or intramural leiomyomas with a mean diameter of 10–49 mm at ultrasound scanning before IVF. Patients who previously underwent myomectomy, those with more than five leiomyomas, and those with leiomyoma-related bleeding were excluded. Recruited women who failed to become pregnant were scanned again 3–9 months later to evaluate the modification of leiomyoma dimensions and the possible manifestation of new lesions. Patients failing to refer were interviewed by phone. The local Institutional Review Board approved the study, and each of the recruited patients signed informed consent.

Sonographic appearance of leiomyomas was defined as symmetric, well defined, hypechoic, and heterogeneous masses (8). Three perpendicular diameters were measured for each myoma. Hysterosonography was systematically performed to rule out submucosal location. A leiomyoma with >50% of its diameter bulging out of the uterine contour line was defined as subserous. Intramural fibroids were those mostly within the uterine shape. Leiomyomas distorting the cavity line were defined as submucosal, and patients with these lesions were excluded from the study and referred for myomectomy. All ultrasound scans were performed by only three blinded and skilled physicians. Preliminary experiments showed an inter- and intraobserver variability for the measurement of the leiomyoma size both consistently <20%. They were both 100% when considering the number of lesions.

Patients selected for IVF were monitored and managed according to a standardized clinical protocol as reported elsewhere (11, 12). Cycles were canceled because of poor (fewer than three follicles) or hyperresponse (serum estradiol level >4,000 pg/mL and/or >20 follicles). The sizes of the leiomyoma before and after treatment were compared using the paired Student t test. Probability values of <.05 were considered to be statistically significant. A binomial distribution model was used to determine the 95% confidence interval (CI) of proportions. The sample size was calculated setting the type I and type II errors at 0.05 and 0.20 respectively and based on a per-patient basis (thus initially assuming that there was only one lesion per patient). We stated an increase in size in one-half of the cases to be clinically relevant. In fact, because some variability in measurement has to be expected (50% of unchanged cases may be found to be erroneously increased and 50% erroneously decreased), this would translate...
One hundred nineteen women with subserosal and intramural leiomyomas were initially considered: 35 were subsequently excluded (12 for submucosal localization and 23 because they got pregnant through IVF). Eighty-four patients were therefore eligible. Twelve patients did not refer for follow-up and were interviewed by telephone: Three patients dropped out for medical reasons and nine for personal reasons. None were operated on or reported any fibroid-related complication. Overall, 72 women completed the study protocol. Thirty-seven women (51%) had only one leiomyoma, and the remainder had two or more lesions. Overall, 138 leiomyomas were available for data analysis. Sixty-eight (49%) were subserosal, and 70 (51%) were intramural. The mean ± SD time between the two echographic evaluations was 5.6 ± 3.4 months. The mean ± SD age and duration of infertility were 37.3 ± 2.8 and 3.3 ± 2.8 years, respectively. The mean ± SD BMI was 22.6 ± 3.8 kg/m². Eighteen women (25%) had previous pregnancies. Indications to IVF cycle were male factor, endometriosis, unexplained infertility, and tubal factor in 38 (53%), 14 (19%), 8 (11%), and 12 (17%) cases, respectively. Forty-one women (57%) were administered a long protocol and 31 (43%) were treated with a protocol with GnRH antagonists. Numbers of canceled cycles for poor and hyperresponse were 8 (11%) and 11 (15%), respectively. The mean ± SD dosage of gonadotropins used was 2,537 ± 1,386 IU, and the mean ± SD duration of stimulation was 10.1 ± 2.3 days. The mean ± SD value of serum E₂ at the time of hCG injection was 1,726 ± 951 pg/mL.

None of the recruited women underwent surgery for leiomyoma between the two examinations. When considering only the bigger lesion per patient, the mean ± SD diameters of the myomas before and after the IVF cycle were 20.5 ± 9.5 and 20.6 ± 10.2 mm, respectively (P=.97; mean difference 0.1 mm, 95% CI −1.3 to 1.3 mm). When considering all lesions, they were 18.2 ± 8.1 and 18.3 ± 8.7 mm, respectively (P=.71; mean difference 0.1 mm, 95% CI −0.6 to 0.9 mm). The impact of IVF on leiomyoma dimension according to ovarian responsiveness, location, and size is shown in Table 1. Development of a new leiomyoma was observed in five women (7%, 95% CI 2% to 15%). The mean ± SD diameter of these new lesions was 11.8 ± 1.8 mm. Distribution of these cases according to the ovarian responsiveness was as follows: 2 out of 23 (9%) among low responders (retrieval of fewer than four oocytes), 2 out of 19 (10%) among moderate responders (retrieval of four to six oocytes), and 1 out of 9 (11%) among high responders (retrieval of more than six oocytes; P=1.00).

In this study, we showed that ovarian hyperstimulation for IVF does not modify the dimension of subserosal and intramural leiomyomas. In line with this finding, we also failed to observe any relationship with the magnitude of the ovarian responsiveness (Table 1). Surprisingly, there was a statistically significant increase only in the group of poor responders. This group was expected to exhibit only a minor increase. In our opinion, this may be due to a type I error. Our data also documented the development of a new leiomyoma in five women (7%, 95% CI 2% to 15%). This latter result is difficult to interpret. The lack of an evident relationship with ovarian responsiveness does not support a causal relationship, but further evidence is required. A study aimed to definitely disentangle this specific issue should also include disease-free women at the time of IVF.

Some limitations of the present study should be considered. First, the diagnosis of leiomyomas was merely by ultrasound. However, many studies have validated transvaginal sonography as a reliable technique in differentiating leiomyomas from other pelvic conditions (8). Moreover, to further reduce possible misdiagnoses, all ultrasound scans were performed by only three highly expert physicians and only women with no more than five lesions were included.

### TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of lesions</th>
<th>Diameter (mm) Pre-IVF</th>
<th>Diameter (mm) Post-IVF</th>
<th>P value</th>
<th>Difference (mm) Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responsiveness to hyperstimulation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>42</td>
<td>19.4 ± 10.4</td>
<td>20.6 ± 11.4</td>
<td>0.04</td>
<td>1.2</td>
<td>0.1 to 2.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>39</td>
<td>17.4 ± 9.1</td>
<td>17.9 ± 6.1</td>
<td>0.22</td>
<td>0.6</td>
<td>−0.4 to 1.5</td>
</tr>
<tr>
<td>High</td>
<td>12</td>
<td>17.5 ± 9.5</td>
<td>16.6 ± 7.5</td>
<td>0.19</td>
<td>−0.9</td>
<td>−2.4 to 0.6</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Subserosal</td>
<td>68</td>
<td>21.5 ± 8.8</td>
<td>21.8 ± 9.5</td>
<td>0.71</td>
<td>0.3</td>
<td>−1.1 to 1.7</td>
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<tr>
<td>Intramural</td>
<td>70</td>
<td>14.9 ± 6.0</td>
<td>15.0 ± 6.1</td>
<td>0.94</td>
<td>0.1</td>
<td>−0.7 to 0.8</td>
</tr>
<tr>
<td><strong>Dimension (diameter), mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>95</td>
<td>14.0 ± 3.2</td>
<td>14.5 ± 4.2</td>
<td>0.15</td>
<td>0.5</td>
<td>−0.2 to 1.1</td>
</tr>
<tr>
<td>20–29</td>
<td>31</td>
<td>23.4 ± 3.0</td>
<td>23.5 ± 7.3</td>
<td>0.90</td>
<td>0.1</td>
<td>−1.9 to 2.2</td>
</tr>
<tr>
<td>≥30</td>
<td>12</td>
<td>37.7 ± 8.5</td>
<td>35.3 ± 10.9</td>
<td>0.42</td>
<td>−2.3</td>
<td>−8.5 to 3.8</td>
</tr>
</tbody>
</table>

**Note:** Data are presented as mean ± SD. Differences were analyzed using paired Student t test and confirmed by Wilcoxon test for paired data. CI = confidence interval.

a Data refer to patients performing oocyte retrieval. Responsiveness to hyperstimulation was categorized as follows: Low: retrieval of <4 oocytes; moderate: retrieval of 4–6 oocytes; high: retrieval of >6 oocytes.

b Data refer to the entire cohort of patients.

**Benaglia.** Correspondence. Fertil Steril 2011.
A second possible limitation of this study is related to the time point for the second evaluation. It can be argued that a 3–9-month period is too short to exclude long-term detrimental effects. On the other hand, fibroids may enlarge over time. Therefore, a study aiming to rule out long-term effects should include a control group of untreated women. This kind of control is of little value in the context of the present findings, because we failed to demonstrate any modification, but it would be mandatory in future studies aiming to investigate the long-term effects of hyperstimulation. A further possible criticism of our study design is related to the relatively large time period for the second assessment. Even if we have to recognize that a fixed period would have been more scientifically appropriate, we chose a 3–9-month period to reduce dropouts. Indeed, only nine women did not refer for second ultrasonography.

In contrast, the study has at least two important strengths. First, it is a prospective study. Second, the large sample size allowed reliable subgroup analyses. For example, failure to identify a relationship with ovarian responsiveness represents an important result of the study, because it reinforces the conclusion that the risk of an IVF-related growth of subserosal and intramural leiomyomas would not be a concern.

REFERENCES