# Decidualization of Endometriosis in a Cohort of IVF-Mediated Pregnancies

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# Abstract

Decidualization is the process of endometrial change in pregnancy, a phenomenon that can involve also ovarian endometriomas. However, the frequency of this event remains unknown. In addition, there is no evidence on the decidualization of deep invasive endometriosis (DIE). To shed more light on this issue, we prospectively recruited women with ovarian endometriomas or DIE who underwent IVF. They were subsequently excluded if they did not become pregnant or if they had a miscarriage. The evaluation was repeated in 5 time points during pregnancy and post-partum. The primary outcome was the rate of decidualized endometriomas at 11-13 weeks' gestation. Data from 45 endometriomas and 15 nodules were available for data analyses. At the 11-13 weeks' ultrasound, endometriomas' decidualization was observed in seven cases, corresponding to 16% (95%CI: 8-29%). Subsequent assessments in pregnancy failed to identify any additional case. DIE also underwent significant changes during pregnancy. An increase in mean diameter (at least 50%), an increase in color score or both were documented in seven, eight and five cases, respectively. In conclusion, **d**ecidualization of ovarian endometriomas in IVF pregnancies is common. DIE may also undergo decidualization, but further evidence is needed for a robust and shared definition of this process.


# Introduction

Decidualization is the process of endometrial change in pregnancy. It is induced mainly by progesterone and creates conditions for implantation and development of early gestation. In women with endometriosis, decidualization may also affect ectopic endometrium.[1]

Decidualized ovarian endometriomas have been described as ovarian cysts with the typical ground glass or low level echogenity that, in addition, show vascularized papillary projections.[2–5] The differential diagnosis between decidualized endometriomas and ovarian cancer (particularly borderline tumors) may be challenging.[4,5] This is clinically relevant because the management radically differs (expectant management with sonographic follow up for endometriomas, immediate surgery even during pregnancy for ovarian cancers). Improving our knowledge on decidualized endometriomas and more precisely estimating the frequency of this event may therefore be helpful for clinical practice. To date, available epidemiological information on this aspect is conflicting and biased. Only data from few retrospective studies focusing on adnexal masses diagnosed in pregnancy were published. [6–8]

In addition, little is known about decidualization of deep infiltrating endometriotic (DIE) nodules.[1,9] We could not find a univocal description of the sonographic features of this process.

In the present study, we report on the sonographic follow up throughout pregnancy of women with endometriosis who achieved pregnancy with IVF. The primary aim of the study was estimating the frequency of sonographic decidualization of endometriomas. The secondary aim was providing a description of ultrasonographic modifications of DIE during pregnancy.

# Materials And Methods

Women undergoing IVF cycles at the Infertility Unit of the Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy between January 2018 and December 2019 were prospectively evaluated for study entry. Inclusion criteria were the following: 1) age between 18 and 43 years, 2) indication to IVF, 3) diagnosis of endometriosis, 4) presence of one or more endometriotic lesions (ovarian endometriomas or deep endometriotic nodules) at the basal transvaginal ultrasound performed prior to initiate the IVF cycle, 5) acceptance to participate (Written Informed consent was obtained from all the participants**)**. Women entering the study were subsequent excluded if they delayed the IVF cycle of more than two months, if they did not become pregnant, if they had a miscarriage before 12 weeks' gestation or if they did not perform at least the assessment scheduled at 11–13 weeks' gestation. Eligible women who were excluded could be re-considered if they entered another IVF cycle. Women could be included more than once if they had more than one pregnancy progressing beyond 12 weeks' gestation. The study was approved by the local Institutional review board (Comitato Etico Milano Area 2). All methods were performed in accordance with the relevant guidelines and regulations.

At the time of enrolment (step 1), women underwent a transvaginal ultrasound to evaluate uterus position and morphology; myometrial features; ovarian dimensions; presence, dimensions and characteristics of ovarian cysts; presence of sonographic soft markers of endometriosis (i.e. site-specific tenderness or fixed ovaries); presence of the "sliding sign" in the pouch of Douglas; presence, dimensions and characteristics of DIE nodules in the anterior and posterior compartment.[10] The evaluation of ovaries and DIE nodules was repeated in 5 more steps: at 6–7 weeks' gestation (step 2), at 11–13 weeks' gestation (step 3), at 23–25 weeks' gestation (step 4), at 35–37 weeks' gestation (step 5) and 30–40 days postpartum (step 6). The assessments at steps 4 and 5 were performed using both transvaginal and transabdominal probes. All the ultrasounds were performed by three expert sonographers (F.A., L.B. and F.F.) with International Ovarian Tumor Analysis (IOTA) certification. They were not blinded to the results of the previous assessments. If possible, women were exclusively scanned by the same sonographer in all the assessments. Remarkable ultrasound images were saved so they could be reviewed and discussed with the other sonographers, if necessary. Mean diameter of the lesions was calculated as the mean of three perpendicular diameters. Vascularization was assessed by color Doppler imaging using a subjective semiquantitative assessment and refers to the whole lesion. A color score of 1 was given when no blood flow was found in the lesion; a color score of 2 when only minimal flow was detected; a color score of 3 when moderate flow was present, and color score of 4 when the lesion appeared highly vascular with marked blood flow. A papillary projection was defined as a solid projection into the cyst cavity from the cyst wall with a height $\geq$ 3 mm.[11]

During the IVF cycle, women were monitored and managed according to a standardized clinical protocol as reported in detail elsewhere.[12] Participation in the study did not modify the standard care in pregnancy.

Decidualization is reported to develop mostly in the first trimester.[2] Moreover, ovarian evaluation in the second and third trimester might not be always possible due to the presence of the pregnant uterus. For these reasons, the main outcome was the rate of decidualized endometriomas at 11–13 weeks' gestation. Secondary outcomes were the evolution of decidualized endometriomas throughout pregnancy and postpartum and modifications of DIE nodules. If a patient had more than one endometrioma on the same ovary, we considered only the largest one. For DIE nodules, we exclusively considered those located in the posterior compartment since their visualization was simpler and deemed more reliable.

Definition of decidualization was previously established for endometriomas (4), the typical feature being the presence of rounded vascularized (color score ≥ 2) papillary projections. Therefore, if a solid component with significant blood flow appeared in an endometriotic cyst at the 11–13 weeks' ultrasound, we deemed the cyst as decidualized. We could not find any sonographic description of decidualized DIE nodules, hence we limited to describe changes in their volume and vascularization throughout pregnancy. Possible definitions of decidualization for deep nodules were arbitrarily proposed *a posteriori* based on the observed findings.

The sample size (about 40 endometriotic cysts) was calculated based on the following assumptions: 1) decidualization rate expected from previous studies: 12% (6,7); 2) wideness of the 95% Confidence Interval (CI): 20% (± 10%).

Data was analyzed using the SPSS software 26.0 (Chicago, IL). Data is reported a mean ± Standard Deviation (SD), or median [interquartile Range (IQR)] or number (%), as appropriate. A binomial distribution model was used to determine the 95%CI of proportions. Student paired *t*-test was used to compare lesion growth between the basal and the 11–13 weeks' assessment.

# Results

One hundred thirty-nine women were initially recruited, of whom 99 were subsequently excluded (87 did not become pregnant or delayed the IVF cycle of more than two months, nine had a first trimester miscarriage and three pregnant cases withdrew consent to participate). Forty pregnancies in 39 women who underwent at least basal and 11-13 weeks' ultrasounds were ultimately included (one woman had two pregnancies). Baseline characteristics of the population are shown in Table 1. Thirty-eight pregnancies (95%) ended in a live birth, one in a therapeutic abortion for a chromosomal anomaly, and one was lost to follow up after the 23-25 weeks' ultrasonographic scan. None of the women required surgery in pregnancy because of endometriosis-related complications and none developed a spontaneous hemoperitoneum in pregnancy (SHiP).

Overall, data from 45 endometriotic cysts and 15 nodules were available for analyses. Eight women had bilateral endometriotic cysts and three had DIE without endometriomas. Basal characteristics of the endometriotic lesions are summarized in Table 2.

When comparing the mean diameter of the endometrioma between basal and 11-13 weeks' assessments, no significant difference emerged (25 ± 10 vs 24 ± 15 mm, respectively, p=0.63). Seven endometriomas in six women developed vascularized papillary projections at the 11-13 weeks' ultrasound and were deemed decidualized (16%, 95%CI: 8-29%). Figure 1 illustrates one of these cases. Signs of decidualization could not be observed at 6-7 weeks' gestation assessment in any of these seven cases. Three decidualized endometriomas had multiple (three to four) papillary projections and a significant growth of the cyst (increase in diameter of more than 50%). The remaining four had a single vascularised papillary projection and a grossly stable cystic dimension. Among the eight women with bilateral endometriomas, six had no decidualization, one had unilateral decidualization and one had bilateral decidualization. The woman included twice carried endometriomas in both pregnancies and never showed signs of decidualization. Decidualization exclusively occurred in women who had fresh embryo transfer (6/28) whereas this phenomenon was never observed among those who had frozen embryo transfer (0/12). However, the difference was not statistically significant (Fisher Exact test, p=0.15).

Thirty-six women (90%) underwent the 23-25 weeks' ultrasound, 32 women (80%) the 35-37 weeks' ultrasound and 33 women (82%) the post-partum ultrasound. We failed to document new cases of decidualization after the 11-13 weeks' assessment. The presence and modification of sonographic signs of endometriomas' decidualization during the study period is presented in details in Table 3. Vascularized papillary projections regressed after delivery in all cases. None of the seven included cysts had a significant volume growth after 11-13 weeks' gestation. When considering post-partum assessments in all women with endometriomas (data available for 30 women, corresponding to 37 cysts), lesions could not be identified in 12 cases (32%).

Four of the 15 DIE nodules could not be identified at the 11-13 weeks' ultrasound as well as in subsequent scans in pregnancy. One of these four cases occurred in the patient who had bilateral decidualized endometriomas. However, in this case, we cannot exclude that we were just unable to distinguish the DIE nodule because it was in close contact with the two enlarged kissing ovaries carrying the decidualized endometriomas. To note, in this case, the DIE nodule could be easily identified at post-partum assessment, when decidualization of the endometriomas regressed completely. In contrast, in the other three cases that could not be identified in pregnancy, the DIE nodule could not be detected in the post-partum also. The analyses were therefore made for the 11 nodules that could be identified at both the basal and the 11-13 weeks' ultrasound scans. Findings are detailed in Table 4. When comparing measurements made at basal and 11-13 weeks' assessments, a significant difference emerged: the mean diameter grew from 16 ± 4 to 20 ± 6 mm (p=0.001). At the 11-13 weeks' ultrasound, five nodules (45%) showed a significant increase in blood flow (color score changed from 1 to 2 in four nodules and from 1 to 3 in one nodule). One of these cases is illustrated in Figure 1. As opposed to what described for endometriomas, we observed changes also after the 11-13 weeks' assessment. An increase in color score later in pregnancy was documented in three nodules (27%). Based on these findings, possible definitions of DIE decidualization could be a significant increase in mean diameter (at least 50%), an increase in color score (≥ 2) or both. These modifications occurred in seven, eight and five cases, respectively. Considering the denominator of 15 women, the corresponding incidences (95%CI) would be 47% (25-

70%), 53% (30-75%) and 33% (15-58%), respectively. DIE lesions could not be visualized in two out of the nine women who performed the post-partum evaluation.

# Discussion

Decidualization of ovarian endometriomas in pregnancy is not rare. In our prospective study, this phenomenon occurred in seven out of 45 endometriomas, corresponding to 16% (95%CI: 8–29%). In addition, our study confirms previous findings suggesting that decidualization of ovarian cysts essentially develops during the first trimester of pregnancy, remains steady or regress during the second trimester of pregnancy and consistently disappears after delivery.[1,2,7]

Three previous retrospective studies reported on the incidence of endometriomas' decidualization. Our results are in line with the rates reported by Ueda *et al.*,[6] and Pateman *et al.*[7], but higher that what reported by Bailleux *et al.*.[8] Combining all these three reports with our findings (in total 15 decidualizations out of 151 endometriomas) allows to estimate that the frequency of decidualization would be about 10% (95%CI: 6–16%), i.e. one out of 10 cases.

The awareness that endometrioma decidualization is relatively common should be kept in mind when vascularized projections suddenly develop at the beginning of pregnancy in women knowing to carry ovarian endometriomas. Decidualization rather than cancer degeneration is by far the most plausible explanation in these cases and women should be reassured. However, this element may be less valid in natural compared to IVF pregnancies because women who conceive spontaneously are not always aware of carrying an endometrioma. In these cases, an in-depth sonographic evaluation in referral centers is needed to minimize misdiagnoses.

The natural history of DIE nodules in pregnancy partly differed from ovarian endometriomas. Firstly, in four cases, we were unable to identify the lesions. The short time interval between the basal and first assessment that was done at 6–7 weeks' gestation tends to rule out the possibility of resorption of the lesions. We initially interpreted this evidence as a consequence of a modification of the echogenicity, a change that can impair the capacity to distinguish them from the surrounding organs. However, this explanation contrasts with the observation that lesions could not be detected in three cases after delivery. A false positive diagnosis at basal ultrasound is an alternative explanation that we cannot exclude.[13] Secondly, we observed a significant growth of the lesions and an enhanced vascularization in a consistent proportion of DIE cases. Even if our statistical power is insufficient for robust conclusions, the frequency of these changes appears more frequent than for endometriomas. Thirdly, these modifications tend to progress over pregnancy rather than self-limiting at the end of the first trimester, as observed for endometriomas. Interestingly, Coccia *et al.* studied three women with DIE during pregnancy and also reported a progressive growth of the nodules up to 24 weeks' gestation, but then a progressive regression.[9] No data was reported on vascularization. Based on our findings, we suggest to define DIE decidualization as an increase in mean diameter of the nodules of more than 50% associated with an increase of color score. To note, as in general blood flow cannot be found in DIE lesions (color score = 1),

this latter criterion could be changed into detection of a color score ≥ 2. Admittedly, this definition of DIE decidualization is arbitrary. A more valid definition would be based on clinical consequences, i.e., the definitions of changes that are associated with increased risk of pregnancy complications.[14–16]

Decidualization of endometriosis in pregnancy is enigmatic and intriguing. Why do most changes occur in the first trimester? Why does decidualization occur in some but not all lesions? Our study cannot address these important queries. Nonetheless, the observation that in a woman with bilateral endometriomas decidualization was observed in only one cyst suggests that this event is lesion- rather than patient-specific. Similarly, even if our definition of DIE decidualization needs confirmation, we observed women who had DIE but not endometrioma decidualization and the other way round. One may speculate that this could depend on the relative component of endometrial cells and fibrosis within the lesions.[17] Possibly, decidualization could occur also in cases with higher fibrotic component but being so limited it is undetectable at ultrasound. Another possibility is that endometriotic cells of different lesions may differently respond to pregnancy hormones. One may speculate that older lesions could be less sensitive. Biological evidence to support these pathogenic hypotheses is however lacking.

Some limitations of our study deserve to be commented. Firstly, we lack the histological confirmation of the diagnosis of decidualization, as none of the included patients underwent surgery for endometriosis during the follow-up. We also lack histological confirmation of endometriosis. However, this second limitation is of doubtful relevance given the elevated accuracy of transvaginal ultrasound, in particular in experienced hands.[18] Secondly, reliability of ultrasounds to monitor ovarian lesions during pregnancy is not validated. This limitation is particularly relevant for the assessments performed in the second part of pregnancy because of the presence of the enlarged uterus that can hide the lesions or complicate their visualization. In fact, the transabdominal approach was commonly required in advanced pregnancy. Thirdly, all the included pregnancies were achieved with IVF. This gave us the possibility to have an ultrasound evaluation just before pregnancy, thus providing accurate evaluations. However, caution is warranted prior to generalize our conclusions to the whole population of women with endometriotic lesions. We cannot exclude a synergistic effect of ovarian hyper-stimulation (and thus the presence of multiple corpora lutea) and pregnancy. There is some biological evidence supporting this possibility.[19,20] To note, in our series, all the decidualized endometriomas were observed among women who had fresh embryo transfer (thus being exposed to ovarian hyperstimulation) and none among those achieving pregnancy with frozen embryos. However, this difference was not statistically significant.

In conclusion, decidualization of ovarian endometriomas in pregnancy is common. A correct diagnosis is essential to avoid useless and possibly harmful surgery. In addition, our study shows that also DIE nodules can undergo important modifications during pregnancy that can be detected at ultrasounds, in particular the increase in vascularisation. Further evidence is needed to clarify the possible additive effect of ovarian hyper-stimulation and to draw a shared definition of DIE decidualization.

# Declarations

**Competing interests:** Dr. Somigliana reports grants from Ferring, grants and personal fees from Merck-Serono, grants and personal fees from Theramex and Gedeon-Richter, outside the submitted work. All the other authors do not have any Conflict of interest to declare.

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**Authors contributions:**

F.F. and E.S. designed the study and wrote the first draft. M.R. performed the statistical analyses. L.B., F.A., I.L.V. and R.B. collected the data and gave substantial contributions to improve the first draft. P.V. supervised the whole study. All the authors repeatedly corrected the different drafts and approved the last version.

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# Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

# Figures

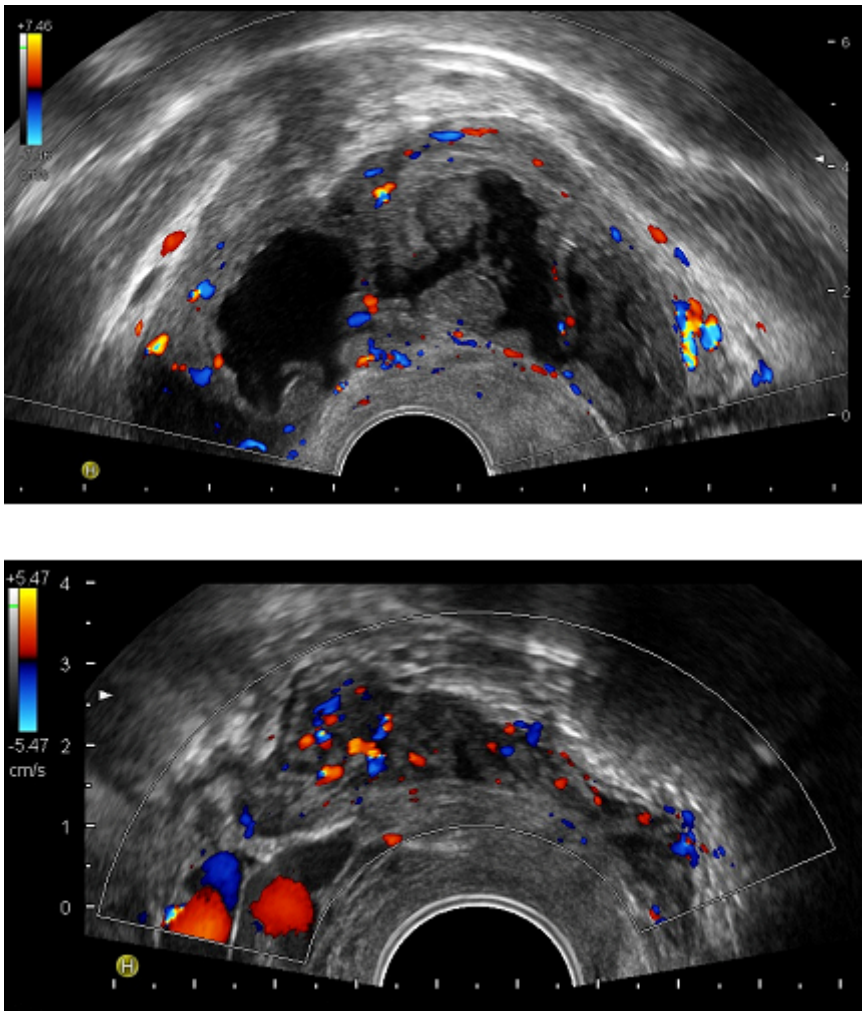


**Figure 1**

Decidualization of ovarian endometriomas and deep peritoneal nodules. In the upper panel, a decidualized endometrioma at 12 weeks' gestation is shown (Case 6 left, see Table 3). Multiple vascularised papillary vegetations can be observed. Their color score was quoted as 2. In the lower panel, a retrocervical endometriotic nodule at 23 weeks' gestation is represented (Case 15, see Table 4). The mean diameter of the lesion increased from basal evaluation to 23 weeks' gestation from 25 to 29 mm. Doppler evaluation showed a color score of 3 (at baseline it was 1).

# Supplementary Files

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- Tables.pdf