HIGH TECH
ENDOMETRIOSI ED INFERTILITÀ

“ASPETTI ETICI E LEGALI”

Roma, 04 Marzo 2009
Ferdinando Dr. Gargiulo
Specialista in Ostetricia e Ginecologia
CTU presso il Tribunale di Roma
The recommendation above is based on a systematic review but the working group noted that endometriosis does not adversely affect pregnancy rates in some large databases (e.g. SART and HFEA) (Templeton et al., 1996). A systematic review indicated that pregnancy rates are lower in women undergoing IVF treatment with endometriosis than in women with tubal infertility (Barnhart et al., 2002). The review included 22 studies, consisting of 2,377 cycles in women with endometriosis and 4,383 in women without the disease. After adjusting for confounding variables, there was a 35% reduction in the chance of achieving pregnancy with IVF in women with endometriosis (OR, 0.63; CI, 0.51-0.77). Other outcome parameters, e.g. fertilization rate, implantation rate, mean number of oocytes retrieved and peak oestradiol concentration were also significantly lower in women with endometriosis compared to those with tubal factor infertility. The data therefore suggest that the presence of endometriosis affects multiple factors determining reproductive success during IVF. It has to be noted that endometriosis does not adversely affect pregnancy rates in some large databases (e.g. SART and HFEA) (Templeton et al., 1996) .......[omissis]
Dichiarazione di Consenso Informato
Per Procreazione Medicalmente Assistita

Ai sensi della legge 19 febbraio 2004, N. 40

- 7. Possibili effetti collaterali sanitari conseguenti all’applicazione della tecnica:

- nelle pazienti affette da endometriosi non si può escludere che ripetute stimolazioni farmacologiche delle ovaie mediante gonadotropine possano determinare una recrudescenza della stessa.

- Non esiste a tutt’ora dopo oltre quarant’anni dell’uso routinario dei farmaci utilizzati per l’induzione dell’ovulazione l’evidenza che questi possono aumentare il rischio di tumori all’ovaio alla mammella (Fertil. Steril vol.83 N.2 2005)
The ESHRE Guideline on Endometriosis 2008

Since endometriosis is an oestrogen-dependant disease, there is concern about the negative impact of supra-physiological oestradiol levels during COH. A retrospective cohort study including 67 infertility patients after surgery for endometriosis stage MI or IV showed a significantly lower cumulative endometriosis recurrence rate (CERR) in patients treated with IVF only compared to patients treated with IDI. Moreover, CERR before and after assisted reproductive technology were similar, suggesting that cumulative exposure to high levels of oestradiol during ovarian hyper stimulation is not a risk factor for endometriosis recurrence (D’Hooghe et al., 2006). However, rare case reports have described increased growth and recurrence of endometriotic lesions during COH and the onset of severe symptoms coincided with high levels of plasma oestradiol (Renier et al., 1995; Govaerts et al., 1998; Anaf et al., 2000, Jun and Lathi, 2007, Ref 12316).

### Table

| Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF (D’Hooghe et al., 2006). | Evidence Level 2a |
Is the endometriosis recurrence rate increased after ovarian hyperstimulation?


- Is the endometriosis recurrence rate increased after ovarian hyperstimulation?
- D’Hooghe TM, Denys B, Spiessens C, Meuleman C, Debrock S.
- Leuven University Fertility Center, Department of Obstetrics and Gynecology, University Hospital Gasthuisberg, Leuven, Belgium. thomas.dhooghe@uz.kuleuven.ac.be

OBJECTIVE: To test the hypothesis that the cumulative endometriosis recurrence rate (CERR) after fertility surgery for endometriosis stage III or IV is increased in women exposed to very high E(2) levels during ovarian hyperstimulation (OH) for IVF when compared with women exposed to less high E(2) levels during OH for intrauterine insemination (IUI).

DESIGN: Retrospective cohort study including infertility patients with endometriosis stage III or IV.


PATIENT(S): Patients (n = 67) with endometriosis stage III (n = 45) or IV (n = 22) who underwent pelvic reconstructive surgery and subsequently started fertility treatment with either IVF only (n = 39), both IVF and IUI in different cycles (n = 11), or IUI only (n = 17).

INTERVENTION(S): Life table analysis was used to calculate the CERR. MAIN OUTCOME MEASURE(S): The CERR based on histologic or cytologic proof of disease recurrence.

RESULT(S): At 21 months after the start of OH the overall CERR was 31% and was significantly lower in patients treated with IVF only (7%) or women treated with both IVF and IUI in different cycles (43%) than in those treated with IUI only (70%). At 36 months after the start of OH, the overall CERR was 63%.

CONCLUSION(S): In contrast to our hypothesis, the results from this study showed that the CERR is lower after ovarian hyperstimulation for IVF than after lower-dose ovarian stimulation for IUI, suggesting that temporary exposure to very high E(2) levels in women during OH for IVF is not a major risk factor for endometriosis recurrence in women treated with assisted reproductive technology.
Pelvic pain after gonadotropin administration as a potential sign of endometriosis.


Pelvic pain after gonadotropin administration as a potential sign of endometriosis.

Jun SH, Lathi RB.

Department of Reproductive Endocrinology and Infertility, Stanford University Medical Center, Stanford, California 94305, USA.

We describe five patients who developed significant pelvic pain, requiring narcotics, during a controlled ovarian hyperstimulation cycle and who were surgically diagnosed with significant endometriosis. Severe pain, especially if it requires narcotics, is unusual for patients undergoing controlled ovarian hyperstimulation and may be an indicator of endometriosis.
Sigmoid endometriosis and ovarian stimulation


- Sigmoid endometriosis and ovarian stimulation.
- Department of Gynaecology, Hospital Erasme, Universite Libre de Bruxelles (ULB), Brussels, Belgium.
- In-vitro fertilization (IVF) and ovarian stimulation are frequently performed in patients with endometriosis. Although endometriosis is a hormone-dependent disease, the rate of IVF complications related to endometriosis is low. We report four cases of severe digestive complications due to the rapid growth of sigmoid endometriosis under ovarian stimulation. In three patients, sigmoid endometriosis was diagnosed at laparoscopy for sterility. Because of the absence of digestive symptoms or repercussion on the bowel, no bowel resection was performed before ovarian stimulation. All patients experienced severe digestive symptoms during ovarian stimulation, and a segmental sigmoid resection had to be performed. Analysis of endoscopic and radiological data demonstrated that bowel lesions of small size may rapidly enlarge and become highly symptomatic under ovarian stimulation. At immunohistochemistry, these infiltrating lesions displayed high populations of steroid receptors and a high proliferative index (Ki-67 activity), suggesting a strong dependence on circulating ovarian hormones and a potential for rapid growth under supraphysiological oestrogen concentrations. Clinicians should be aware of this rare but severe digestive complication of ovarian stimulation. The early diagnosis of such lesions may help the patients to avoid months of morbidity falsely attributed to ovarian stimulation side effects. Further experience is necessary to determine the optimal attitude when diagnosing a small and asymptomatic endometriotic bowel lesion before ovarian stimulation.
IVF AND ENDOMETRIOSIS

- **Human Reproduction**, Vol. 15, No. 4, 790-794, April 2000
  © 2000 European Society of Human Reproduction and Embryology

- **Sigmoid endometriosis and ovarian stimulation: Case reports**
- **Vincent Anaf1,4, Issam El Nakadi2, Philippe Simon1, Yvon Englert1, Marie-Odile Peny3, Isabelle Fayt3 and Jean-Christophe Noel3**
- 1 Departments of Gynaecology, 2 Digestive Surgery and 3 Pathology, Hospital Erasme, Universite Libre de Bruxelles (ULB), Brussels, Belgium
- In-vitro fertilization (IVF) and ovarian stimulation are frequently performed in patients with endometriosis. Although endometriosis is a hormone-dependent disease, the rate of IVF complications related to endometriosis is low. **We report four cases of severe digestive complications due to the rapid growth of sigmoid endometriosis under ovarian stimulation.** In three patients, sigmoid endometriosis was diagnosed at laparoscopy for sterility. Because of the absence of digestive symptoms or repercussion on the bowel, no bowel resection was performed before ovarian stimulation. All patients experienced severe digestive symptoms during ovarian stimulation, and a segmental sigmoid resection had to be performed. Analysis of endoscopic and radiological data demonstrated that bowel lesions of small size may rapidly enlarge and become highly symptomatic under ovarian stimulation. At immunohistochemistry, these infiltrating lesions displayed high populations of steroid receptors and a high proliferative index (Ki-67 activity), suggesting a strong dependence on circulating ovarian hormones and a potential for rapid growth under supraphysiological oestrogen concentrations. Clinicians should be aware of this rare but severe digestive complication of ovarian stimulation. The early diagnosis of such lesions may help the patients to avoid months of morbidity falsely attributed to ovarian stimulation side effects. Further experience is necessary to determine the optimal attitude when diagnosing a small and asymptomatic endometriotic bowel lesion before ovarian stimulation.

- **Key words:** deep infiltrating endometriosis/IVF complication/ovarian stimulation/sigmoid endometriosis
Results of IVF in women with endometriosis

  - [Results of IVF in women with endometriosis]
  - [Article in French]
  - Olivennes F.
  - Service de Gynécologie-Obstétrique et de Médecine de la Reproduction, Hôpital Cochin, Paris, France.
  - When associated with infertility, endometriosis often requires in vitro fertilization (IVF). The need of IVF instead of other Assisted Reproductive Technologies is correlated with the severity of the lesions and associated tubal pathology. Results of IVF (in terms of pregnancy rates), are influenced by the existence of endometriosis, but this influence remains controversial, and focused on three possible points: poor ovarian reserve (and ovarian response), poor quality of oocytes and embryos, poor implantation. It seems that mild and moderate endometriosis (I-II American Fertility Society score) has few deleterious effect on ovarian reserve, ovarian response, and pregnancy rates. All these parameters are decreased by the existence of severe endometriosis (III-IV AFS). Its surgical treatment appears to improve the results of IVF, notably in women under 35. But iterative surgery of endometriomas might be deleterious for ovarian function. Previous treatment by Gn-RH agonists also improves the outcome of IVF, whereas ICSI does not modify either the biological parameters, nor the pregnancy rates. Ovarian hyperstimulation in women with endometriosis might increase the severity of the lesions and the risk of complications: the use of unstimulated cycle (n-IVF) in young patients with normal ovarian reserve might be interesting.
Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation-intrauterine insemination or in vitro fertilization-embryo transfer.


- Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation-intrauterine insemination or in vitro fertilization-embryo transfer.
- Dmowski WP, Pry M, Ding J, Rana N.
- Institute for the Study and Treatment of Endometriosis, Oak Brook, Illinois, USA. wpdmowski@oakbrookfertility.com
- OBJECTIVE: To compare controlled ovarian hyperstimulation-intrauterine insemination (COH-IUI) or IVF-ET pregnancy rates per cycle (PR) and cycle and cumulative fecundity (f and cf) with COH-IUI or IVF-ET in endometriosis. DESIGN: Retrospective analysis. SETTING: Endometriosis research institute. PATIENT(S): Women with endometriosis and infertility (n = 313) who underwent consecutive COH-IUI (202 patients, 648 cycles), IVF-ET (111 patients, 139 cycles), or IVF-ET after failed COH-IUI (56 patients, 68 cycles). INTERVENTION(S): None. MAIN OUTCOME MEASURE(S): Crude PR and life table-estimated f and cf. RESULT(S): With COH-IUI, 69 patients conceived; 65 conceived with IVF-ET; and 30 conceived with IVF-ET after COH-IUI (PR 11%, 47%, and 44%). With COH-IUI, six-cycle cf was 41%, and f for cycles 1-6 was 15%, 12%, 8%, 7%, 7%, and 0. With IVF-ET, three-cycle cf was 73%, whereas f for cycles 1-3 was 47%, 27%, and 33%. First-cycle f with IVF-ET was significantly higher than cf of six COH-IUI cycles. When the data were stratified according to the stage of endometriosis and women's age, the benefit of IVF over COH was even more pronounced. Prior COH-IUI failure did not adversely affect IVF-ET outcome. CONCLUSION(S): In endometriosis, PR, f, and cf are significantly higher with IVF-ET than COH-IUI, especially in stage IV and in women >38 years of age. Considering adverse effects of prolonged ovarian stimulation on endometriosis, IVF-ET should be the first-line approach in the management of infertility in this disease. If COH-IUI is attempted, it should not exceed three to four cycles.
Ovarian response to repeated controlled stimulation in in-vitro fertilization cycles in patients with ovarian endometriosis.

Ovarian response to repeated controlled stimulation in in-vitro fertilization cycles in patients with ovarian endometriosis.
Al-Azemi M, Bernal AL, Steele J, Gramsbergen I, Barlow D, Kennedy S.
Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford Radcliffe Hospital, Women's Centre, Oxford, OX3 9DU, UK.

In-vitro fertilization (IVF) is an effective infertility treatment for women with endometriosis, but most women need to undergo several cycles of treatment to become pregnant. This case-control study was designed to assess how consistently women with ovarian endometriosis respond to ovarian stimulation in consecutive treatment cycles compared to women with tubal infertility. We compared outcome measures in 40 women with a history of surgically confirmed ovarian endometriosis and 80 women with tubal infertility, all of whom had at least three IVF treatment cycles. The groups were matched for age and early follicular follicle stimulating hormone (FSH) concentration at their first IVF cycle. Outcome measures included number of follicles, number of oocytes, peak oestradiol concentration and number of FSH ampoules required per follicle. Cumulative pregnancy and live birth rates were calculated in both groups. The ovarian endometriosis group had a significantly poorer ovarian response and required significantly more ampoules of FSH per cycle, a difference that became greater with each subsequent cycle. However, cumulative pregnancy (63.3 versus 62.6% by fifth cycle) and live birth (46.8 versus 50.9% by fifth cycle) rates were similar in both groups. In conclusion, despite decreased ovarian response to FSH, ovarian endometriosis does not decrease the chances of successful IVF treatment.
Is the endometriosis recurrence rate increased after ovarian hyperstimulation?


- Is the endometriosis recurrence rate increased after ovarian hyperstimulation?
- D'Hooghe TM, Denys B, Spiessens C, Meuleman C, Debrock S.
- Leuven University Fertility Center, Department of Obstetrics and Gynecology, University Hospital Gasthuisberg, Leuven, Belgium. thomas.dhooghe@uz.kuleuven.ac.be

OBJECTIVE: To test the hypothesis that the cumulative endometriosis recurrence rate (CERR) after fertility surgery for endometriosis stage III or IV is increased in women exposed to very high E(2) levels during ovarian hyperstimulation (OH) for IVF when compared with women exposed to less high E(2) levels during OH for intrauterine insemination (IUI).

DESIGN: Retrospective cohort study including infertility patients with endometriosis stage III or IV. SETTING: Leuven University Fertility Center, between 1990 and 2001. PATIENT(S): Patients (n = 67) with endometriosis stage III (n = 45) or IV (n = 22) who underwent pelvic reconstructive surgery and subsequently started fertility treatment with either IVF only (n = 39), both IVF and IUI in different cycles (n = 11), or IUI only (n = 17).

INTERVENTION(S): Life table analysis was used to calculate the CERR. MAIN OUTCOME MEASURE(S): The CERR based on histologic or cytologic proof of disease recurrence. RESULT(S): At 21 months after the start of OH the overall CERR was 31% and was significantly lower in patients treated with IVF only (7%) or women treated with both IVF and IUI in different cycles (43%) than in those treated with IUI only (70%). At 36 months after the start of OH, the overall CERR was 63%. CONCLUSION(S): In contrast to our hypothesis, the results from this study showed that the CERR is lower after ovarian hyperstimulation for IVF than after lower-dose ovarian stimulation for IUI, suggesting that temporary exposure to very high E(2) levels in women during OH for IVF is not a major risk factor for endometriosis recurrence in women treated with assisted reproductive technology.
The outcome of in vitro fertilization and embryo transfer therapy in women with endometriosis failing to conceive after laparoscopic conservative surgery.


**Huang HY, Lee CL, Lai YM, Chang MY, Chang SY, Soong YK.**

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Chang Gung Medical College 5, Fu-Hsing Street, Kwei-Shan, Tao-Yuan, Taiwan, Republic of China.

**STUDY OBJECTIVE:** To compare the outcome of in vitro fertilization and embryo transfer (IVF-ET) after laparoscopic surgery in women with endometriosis with that of patients with tubal factor infertility. **DESIGN:** Retrospective survey of hospital and office charts using a computerized worksheet. **SETTING:** Lin-Kou medical center of Chang Gung Memorial Hospital. **PATIENTS:** Sixty-seven women with minimal to mild or moderate to severe endometriosis. Women with tubal factor infertility without other associated disorders (60 cycles) made up the control group. **INTERVENTIONS:** Seventy-five consecutive cycles of IVF-ET were performed in these patients who failed to conceive after laparoscopic conservative surgery. **MEASUREMENTS AND MAIN RESULTS:** The concentration of serum estradiol on the day of human chorionic gonadotropin (hCG) injection, the day of hCG injection, clinical pregnancy rates per transfer, number of follicles larger than 14 mm, number of embryos transferred, and implantation rate were not significantly different between women with endometriosis and those with tubal factor infertility. The number of oocytes retrieved and number fertilized were decreased, and the basal level of follicle-stimulating hormone on cycle day 3 was higher in women with both degrees of endometriosis. **CONCLUSIONS:** The outcome of IVF-ET in patients with endometriosis after laparoscopic surgery did not differ from that in the group with tubal factor infertility, but the former required more ampules of gonadotropin to achieve the same response. The advantages of laparoscopic surgery in women with endometriosis should be probably correlated with success of IVF-ET.
Cancer risk associated with subfertility and ovulation induction

Cancer Causes Control. 2000 Apr;11(4):319-44. Links

Cancer risk associated with subfertility and ovulation induction: a review.

Klip H, Burger CW, Kenemans P, van Leeuwen FE.

Department of Epidemiology, Netherlands Cancer Institute, Amsterdam.

OBJECTIVE: Over the past decades the use of fertility drugs (FDs) has greatly increased. Recently, the possible association between the use of FDs and risk of cancer has aroused great concern. In this paper, we critically review the available epidemiologic studies.

METHODS: We identified papers published between 1966 and 1999 that examined FDs and specific causes of subfertility in relation to the risks of cancers of the ovary, breast, endometrium and thyroid, and melanoma.

RESULTS: Although present insights into the pathogenesis of hormone-related malignancies suggest a possible association between the use of FDs and the risk of specific cancers, this has not been convincingly demonstrated in epidemiologic studies. With regard to cancer risk in relation to the cause of subfertility, the only consistent association observed is an increased risk of endometrial cancer for women with subfertility due to hormonal disorders. While positive findings in some studies on FDs and ovarian cancer risk have aroused serious concern, the associations observed in most of these reports appear to be due to bias or chance rather than being causal. The most important sources of bias are inadequate confounder control for both parity and causes of subfertility.

CONCLUSIONS: To discriminate between the possible carcinogenic effects of various ovulation induction regimens, subfertility disorders, and reproductive characteristics associated with subfertility, future studies should include large populations of subfertile women with sufficient follow-up time. In such cohort studies the cause of subfertility should be measured adequately (based on medical records) and information about reproductive characteristics should be collected for all cohort members. Such studies should also include a group of subfertile women with an indication for FD use but not so treated.
Concern has been expressed that exposure to fertility drugs might be associated with a risk of ovarian cancer. We have examined the incidence of breast and ovarian cancer in a cohort of 10,358 women referred for in-vitro fertilisation (IVF) treatment in Victoria, Australia, between 1978 and 1992. The "exposed" group (n = 5564) had had ovarian stimulation to induce multiple folliculogenesis and the "unexposed" group (n = 4794) had been referred for IVF but were untreated or had "natural cycle" treatment without ovarian stimulation. Duration of follow-up ranged from 1 to 15 years. Cases of cancer were determined by record linkage with data from population-based cancer registries. 34 cases of invasive breast cancer and 6 of invasive ovarian cancer were observed. A comparison with the expected numbers, derived by applying age-standardised general population rates to the cohort gave standardised incidence ratios (SIR) for breast cancer of 0.89 (95% CI 0.55-1.46) in the exposed group and 0.98 (0.62-1.56) in the unexposed group, and for ovarian cancer SIRs were 1.70 (0.55-5.27) and 1.62 (0.52-5.02), respectively. Rates of all cancers were not significantly different from general population rates. The relative risk (RR) of cancer, adjusted for age and infertility type, was, in the treated group compared with the untreated group, 1.11 (95% CI 0.56-2.20) for breast cancer and 1.45 (0.28-7.55) for ovarian cancer. The risk of body of uterus cancer was increased in the exposed and unexposed groups combined (SIR 2.84 [1.18-6.81]).

Women with unexplained infertility, independent of IVF exposure, had significantly increased risks of ovarian cancer (RR = 19.19 [2.23-165.0]) and body of uterus cancer (RR = 6.34 [1.06-38.0]) compared with women with known causes of infertility. This relatively short-term follow-up suggests that ovarian stimulation with IVF is not associated with an increased risk of breast cancer. Although there was no significantly increased risk of ovarian cancer after ovarian stimulation with IVF the small number of cases limits the conclusions that can be drawn. Longer-term follow-up of large cohorts of women who have been in IVF programmes will be necessary.
Molecular genetic evidence that endometriosis is a precursor of ovarian cancer


Molecular genetic evidence that endometriosis is a precursor of ovarian cancer.


Nuffield Department of Obstetrics and Gynaecology, The Women's Centre, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom. amanda.prowse@obs-gyn.ox.ac.uk

Histopathology and epidemiology studies have consistently demonstrated a strong link between endometriosis and endometriosis-associated ovarian cancers (EAOCs)—in particular, the endometrioid and clear cell subtypes. However, it is still unclear whether endometriosis is a precursor to EAOCs, or whether there is an indirect link because similar factors predispose to both diseases. In order to search for evidence of clonal progression, we analyzed 10 EAOCs (endometrioid=4; clear cell=6) with coexisting endometriosis for common molecular genetic alterations in both the carcinoma and corresponding endometriosis. We used 82 microsatellite markers spanning the genome to examine loss of heterozygosity (LOH) in the coexisting carcinoma and endometriosis samples. A total of 63 LOH events were detected in the carcinoma samples; twenty two of these were also detected in the corresponding endometriosis samples. In each case, the same allele was lost in the endometriosis and cancer samples. Interestingly, no marker showed LOH in the endometriosis alone. These data provide evidence that endometriosis is a precursor to EAOCs. Copyright (c) 2006 Wiley-Liss, Inc.
Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis.


- Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis.
- Zanetta GM, Webb MJ, Li H, Keeney GL.
- Section of Gynecologic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.

OBJECTIVE: Endometriosis is extremely common in developed countries. Obesity is a major health concern and may cause hyperestrogenism. Hormonal replacement, particularly unopposed estrogens after hysterectomy, is becoming popular. Because endometriosis is ectopic endometrium, hyperestrogenism (either endogenous or exogenous) may cause hyperplasia or transformation into cancer. This study was conducted to describe the main clinical and pathologic features of malignancies in endometriosis and define the treatment and outcome and to compare patients who had cancer arising in endometriosis with patients who had endometriosis but no cancer. METHODS: Patients who had tumors from endometriosis diagnosed from 1986 to 1997 were analyzed retrospectively. Each patient was matched with two control patients (endometriosis without cancer) treated during the same study interval. Clinical and epidemiologic variables were compared to identify risk factors for the development of cancer. RESULT: We identified 31 patients with cancer developing from endometriosis. Fifteen women were obese, 9 had a history of endometriosis, and 9 were taking unopposed estrogen. Endometrioid adenocarcinoma was the most common histologic type (16 patients). When the patients with cancer were compared with controls, no significantly higher risk for the development of cancer was found with prolonged use of unopposed estrogens or with higher body mass index, but a trend was observed. When obesity and use of unopposed estrogens were considered together, the difference was statistically significant (P = 0.05).

CONCLUSION: Hyperestrogenism, either endogenous or exogenous, is a significant risk factor for the development of cancer from endometriosis. The prevalences of endometriosis, obesity, and use of hormonal replacement therapy in women in developed countries are increasing, and this trend justifies the assumption that cancer developing in endometriosis might become more common in the future. Copyright 2000 Academic Press.
Malignancy arising in extraovarian endometriosis during estrogen stimulation

  - Malignancy arising in extraovarian endometriosis during estrogen stimulation.
  - Gücer F, Pieber D, Arikan MG.
  - University of Graz, Department of Obstetrics and Gynecology, Austria.
- OBJECTIVE: Endometriosis can undergo estrogen-dependent changes similar to endometrium and may carry a risk of developing hyperplasia and carcinoma during unopposed estrogen stimulation.
- MATERIAL-METHOD: We reviewed the existing literature to analyze the potential of a malignancy arising from extraovarian endometriosis by estrogen stimulation.
- RESULTS: To our knowledge, there are 20 published cases so far, with a malign transformed endometriosis during estrogen stimulation at an extraovarian site. The most common site of malignancy arising from endometriosis was the vagina (n = 5). The most common histological finding was adenocarcinoma (n = 13). The incidence of malignant transformation in extraovarian endometriosis during unopposed estrogen replacement cannot be estimated based upon these case reports.
- CONCLUSION: Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestins to estrogen replacement therapy should be considered in women who have undergone hysterectomy with oophorectomy because of endometriosis, especially if they are known to have residual endometriosis.
Ovarian cancer risk after the use of ovulation-stimulating drugs.

  - Ovarian cancer risk after the use of ovulation-stimulating drugs.
  - Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, Westhoff CL.
  - Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Room 7068, Bethesda, MD 20852-7234, USA. brinton@nih.gov
  - OBJECTIVE: To assess the long-term effects of ovulation-stimulating drugs on the risk of ovarian cancer. METHODS: A retrospective cohort study of 12,193 eligible study subjects (median age 30 years) who were evaluated for infertility during the period of 1965-1988 at 5 clinical sites identified 45 subsequent ovarian cancers in follow-up through 1999. Standardized incidence ratios compared the risk of cancer among the infertile patients to the general population, whereas analyses within the cohort allowed the derivation of rate ratios for drug usage compared with no usage after adjustment for other ovarian cancer predictors. RESULTS: The infertility patients had a significantly elevated ovarian cancer risk compared with the general population (standardized incidence ratio 1.98, 95% confidence intervals [CI] 1.4, 2.6). When patient characteristics were taken into account and risks assessed within the infertile women, the rate ratios associated with ever usage were 0.82 (95% CI 0.4, 1.5) for clomiphene and 1.09 (95% CI 0.4, 2.8) for gonadotropins. There were higher, albeit nonsignificant, risks with follow-up time, with the rate ratios after 15 or more years being 1.48 (95% CI 0.7, 3.2) for exposure to clomiphene (5 exposed cancer patients) and 2.46 (95% CI 0.7, 8.3) for gonadotropins (3 exposed cancer patients). Although drug effects did not vary by causes of infertility, there was a slightly higher risk associated with clomiphene use among women who remained nulligravid, based on 6 exposed patients (rate ratio 1.75; 95% CI 0.5, 5.7). CONCLUSION: The results of this study generally were reassuring in not confirming a strong link between ovulation-stimulating drugs and ovarian cancer. Slight but nonsignificant elevations in risk associated with drug usage among certain subgroups of users, however, support the need for continued monitoring of long-term risks. LEVEL OF EVIDENCE: II-2
Uterine cancer after use of clomiphene citrate to induce ovulation.


Uterine cancer after use of clomiphene citrate to induce ovulation.

Althuis MD, Moghissi KS, Westhoff CL, Scoccia B, Lamb EJ, Lubin JH, Brinton LA.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892-7234, USA. m.althuis@verizon.net

Clomiphene citrate, a selective estrogen receptor modulator, increases estradiol levels and consequently may increase risk of cancer of the uterine corpus. The authors conducted a retrospective cohort study of 8,431 US women (145,876 woman-years) evaluated for infertility during 1965-1988. Through 1999, 39 uterine cancers were ascertained by questionnaire or cancer and death registries. Poisson regression estimated adjusted rate ratios. Study results suggest that clomiphene may increase uterine cancer risk (rate ratio (RR) = 1.79, 95% confidence interval (CI): 0.9, 3.4) and present evidence of a dose response (p(trend) = 0.07) and latency effect (p(trend) = 0.04). Uterine cancer risk increased with clomiphene dose (RR = 1.93, 95% CI: 0.9, 4.0 for >900 mg), menstrual cycles of use (RR = 2.16, 95% CI: 0.9, 5.2 for >or=6 cycles), and time elapsed since initial use (RR = 2.50, 95% CI: 0.9, 7.2 for women followed for >or=20 years). Risk was more strongly associated with clomiphene among nulligravid (RR = 3.49, 95% CI: 1.3, 9.3) and obese (RR = 6.02, 95% CI: 1.2, 30.0) women, with risk substantially elevated among women who were both obese and nulligravid (RR = 12.52, 95% CI: 1.5, 108.0). Clomiphene may increase uterine cancer risk, with higher doses leading to higher risk. Long-term follow-up of infertility cohorts is necessary to clarify the association between clomiphene use and uterine cancer.
Ovulation induction for infertility is it safe or not?

- Anderson SM, Dimitrievich E.
- USD School of Medicine, Canistota, USA.
- Case reports of ovarian tumors in women undergoing fertility treatment have raised questions about the potential neoplastic effects of ovulation-induction agents used in the treatment of infertility. This has been the subject of much debate, media coverage and patient alarm. An increased risk of malignant epithelial ovarian cancer, borderline epithelial ovarian tumors, and nonepithelial ovarian cancer have been reported in association with the use of fertility drugs. Further review of the literature reveals that there are limitations to the studies reporting this association and indicates that further research is needed before a causal relationship can be established.
Ovarian cancer after successful ovulation induction: a case report.


**Hull ME, Kriner M, Schneider E, Maiman M.**
Division of Reproductive Endocrinology, State University of New York at Stony Brook, USA.

**BACKGROUND:** Questions have been raised regarding the potential association of ovulation-inducing drugs and ovarian cancer. Worldwide there have been 13 cases of ovarian carcinoma reported to occur in women previously treated with ovulation-inducing drugs (clomiphene citrate and/or gonadotropins). **CASE:** A 40-year-old woman complained of secondary infertility. She conceived after five cycles of human menopausal gonadotropins with intrauterine insemination. Eight months after cesarean delivery, she presented with right lower quadrant pain and a right adnexal mass. At exploratory laparotomy the patient was found to have a poorly differentiated papillary serous carcinoma of the ovary. **CONCLUSION:** Ovarian carcinoma developed within 18 months of exposure to ovulation-inducing agents, human menopausal gonadotropins. It would be prudent to gather a registry of cases to assess the risk associated with human menopausal gonadotropins with or without gonadotropin-releasing hormone analogs.
Synchronous endometrioid carcinoma of the ovary and endometrium associated with ovulation induction.

- Synchronous endometrioid carcinoma of the ovary and endometrium associated with ovulation induction.
- Ghourab S.
- Department of Obstetrics and Gynecology, King Khalid University Hospital, King Saud University, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. sghourab@ksu.edu.sa
- Over the last 2 decades great concern about the possible association between ovarian cancer and ovulation induction has been raised. Between the first reported case in 1982 and the end of year 2000, there have been 44 cases of ovarian carcinoma reported to occur in women previously treated with ovulation induction drugs. Most of these tumors were of the serous type with low malignant potential. In the present case, the patient had secondary anovulatory infertility and previous left cystoophorectomy for ovarian endometrioma. She was treated with human menopausal gonadotrophin alone or in combination with clomiphene citrate for 13 cycles prior to presentation. Screening ultrasound revealed multicystic right ovarian mass (15 x 9 x 6 cm). Hysterectomy and right salpingo-oophorectomy were carried out. Intraoperative and histological examinations showed stage 1A endometrioid ovarian cancer and well-differentiated endometrial adenoacanthoma with minimal myometrial invasion. A brief but critical review of published literature regarding the association of ovulation induction and increased risk of ovarian cancer is presented.
Two cases of ovarian tumours in women who had undergone multiple ovarian stimulation attempts.


- Two cases of ovarian tumours in women who had undergone multiple ovarian stimulation attempts.
- Grimbizis G, Tarlatzis BC, Bontis J, Miliaras D, Lagos S, Pournaropoulos F, Mantalenakis S.
- 1st Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece.
- Concerns have been raised recently about the possible association between superovulation and ovarian cancer. In order to contribute to the limited literature on this important issue, two cases of ovarian tumours in women who had undergone multiple ovulation inductions are presented. In the first case, the patient had secondary anovulatory infertility. She was treated with human menopausal gonadotrophin (HMG) alone and in combination with clomiphene citrate or buserelin for six cycles. She then underwent ovarian stimulation with buserelin/HMG in the long protocol for in-vitro fertilization (IVF) and embryo transfer. In preparation for a new IVF/embryo transfer attempt, 8 months later, the screening ultrasound revealed a cystic formation of the left ovary and an enlargement of the right. During laparotomy, both ovaries were found to bear large tumours (approximately 6 x 5 x 4 cm) which were removed. Histological examination showed that they were epithelial tumours (serous-papillary cystadenomas) of borderline malignancy. The patient conceived spontaneously 1.5 years after the operation. In the second case, the patient presented with secondary anovulatory infertility. She underwent ovulation induction with clomiphene/HMG and with buserelin/HMG in the long protocol, and intra-uterine insemination with husband's spermatozoa and conceived (singleton pregnancy). She was delivered by Caesarean section, during which a cystic tumour of the left ovary was removed. Histological examination revealed a benign mucous cystadenoma of the ovary.
«La morte di Accursia Attardi è stata determinata dall’ imperizia e negligenza dei medici dell' Imi». Scrivono così i consulenti incaricati dal pm Gianfranco Scarfò di accertare le cause del decesso della trentunenne di Sciacca, avvenuto il 18 aprile 2004 all’ Istituto materno infantile del Policlinico, una settimana dopo il suo rientro da Bologna, dove si era sottoposta alla fecondazione assistita. Per i periti del pubblico ministero - che entro poche settimane chiuderà l’ inchiesta – i medici non assicurarono una corretta assistenza alla paziente affetta da "sindrome da iperstimolazione ovarica": non valutarono i parametri vitali, non misurarono la pressione arteriosa né effettuarono un esame del torace che avrebbe mostrato la presenza di liquido nei polmoni. Tutti accertamenti che fanno parte dei protocolli scientifici schematizzati per questa patologia e che avrebbero
Interrogativi etici e medico-legali

- Allo stato attuale quale informazione possiamo e dobbiamo dare ad una donna infertile affetta da endometriosi?
- A quali rischi la sottoponiamo con le tecniche di PMA attualmente in uso?
- Vi sono alternative?
NON DIMENTICHIAMO MAI PER CHI LAVORIAMO

Grazie dell’attenzione