Φάρμακα γονιμότητας και γυναικολογικός καρκίνος ή καρκίνος του μαστού

Venus, Mars and Cupid, by Piero di Cosimo (c. 1505)

Δρ. ΑΝΑΣΤΑΣΙΑ ΜΠΟΘΟΥ
Επίκουρη Καθηγήτρια Μαιευτικής ΠΑ.Δ.Α

Υπογονιμότητα-Επιδημιολογικά στοιχεία

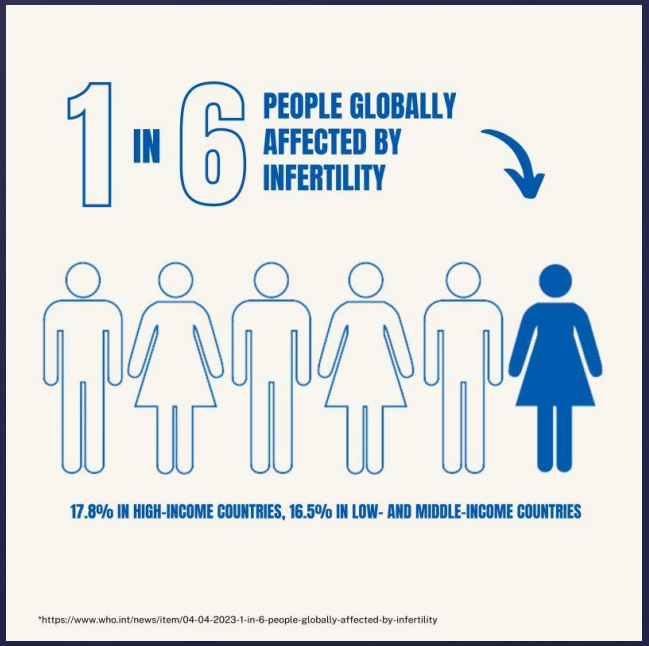
- Η υπογονιμότητα είναι μια διαταραχή της υγείας του ανδρικού ή του γυναικείου αναπαραγωγικού συστήματος, η οποία ορίζεται από την αποτυχία επίτευξης εγκυμοσύνης μετά από 12 ή περισσότερους μήνες τακτικής σεξουαλικής επαφής χωρίς προφυλάξεις.

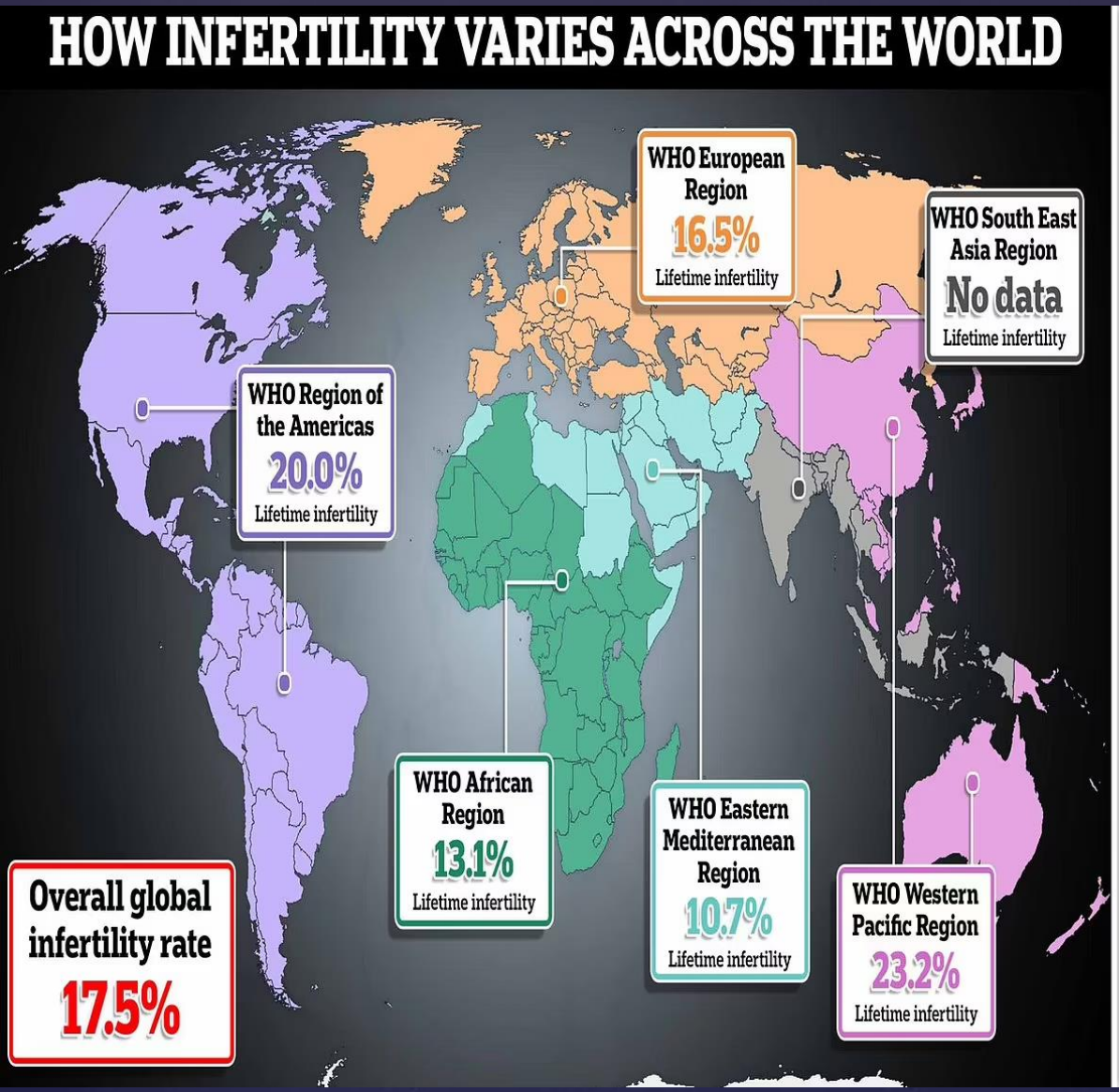
CDC 2023

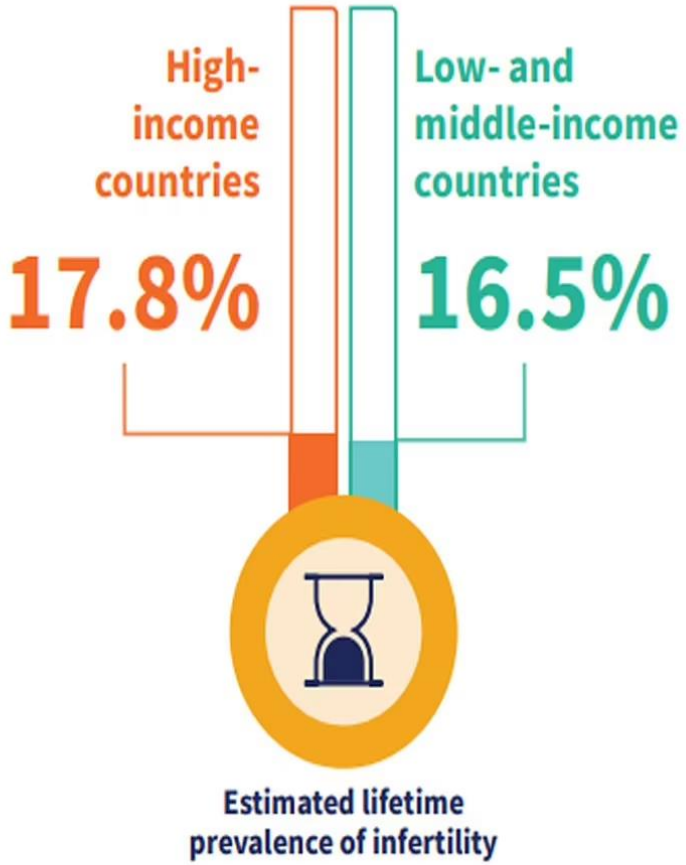
- 17,5% του ενήλικου πληθυσμού (1 στους 6 παγκοσμίως), αντιμετωπίζει πρόβλημα υπογονιμότητας.

WHO 2023

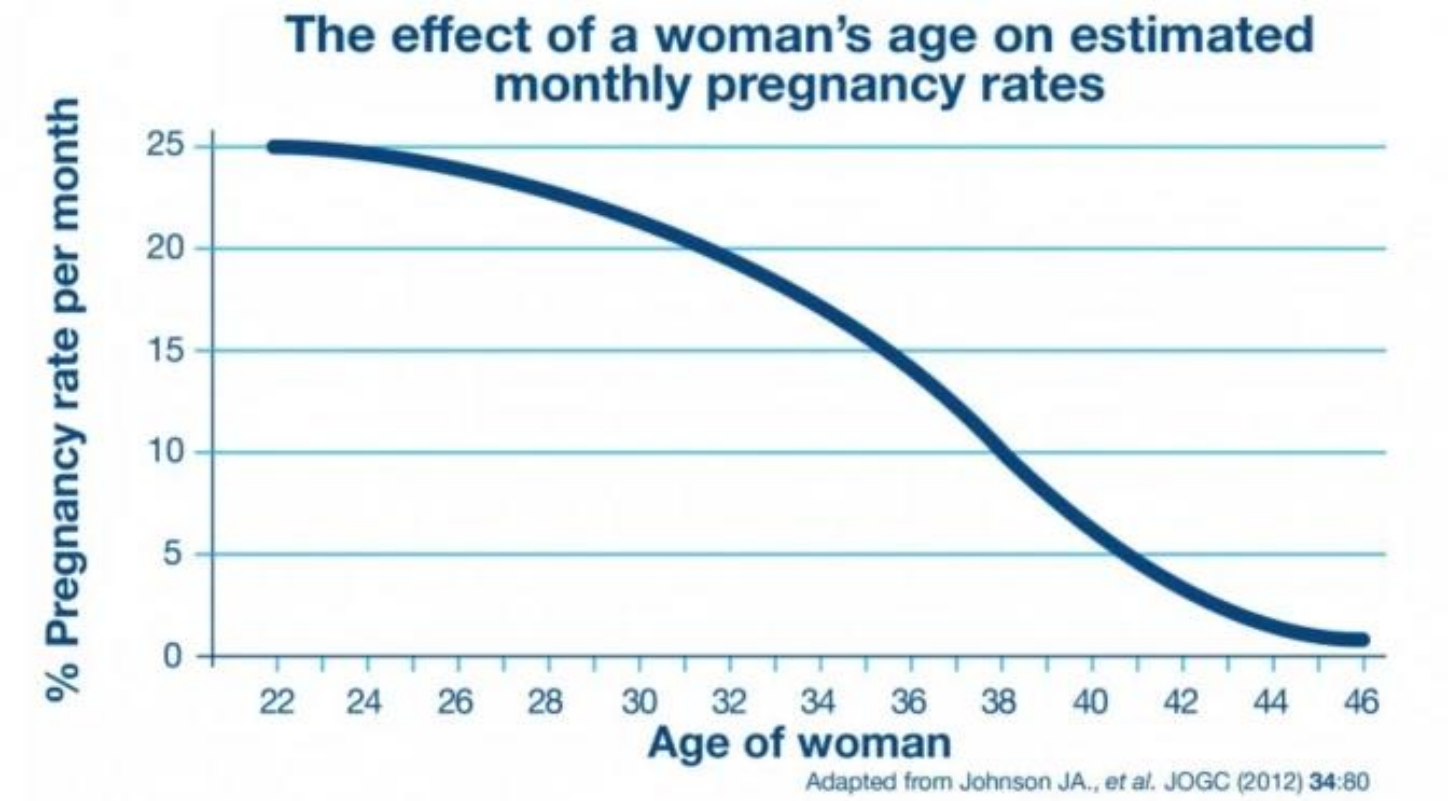
- 19% όλων των ζευγαριών δεν μπορούν να συλλάβουν μετά από ένα χρόνο σεξουαλικών επαφών χωρίς προφυλάξεις.
- 10% όλων των ζευγαριών αδυνατεί να συλλάβει μετά από δύο χρόνια σεξουαλικών επαφών χωρίς προφυλάξεις.
- Δεν υπάρχει ειδικό «προφίλ» του υπογόνιμου ζευγαριού.




HOW INFERTILITY VARIES ACROSS THE WORLD
WHO European Region
16.5%
Lifetime infertility
WHO South East Asia Region
No data
Lifetime infertility
WHO Region of the Americas
20.0%
Lifetime infertility
WHO African Region
13.1%
Lifetime infertility
WHO Eastern Mediterranean Region
10.7%
Lifetime infertility
WHO Western Pacific Region
23.2%
Lifetime infertility
Overall global infertility rate
17.5%

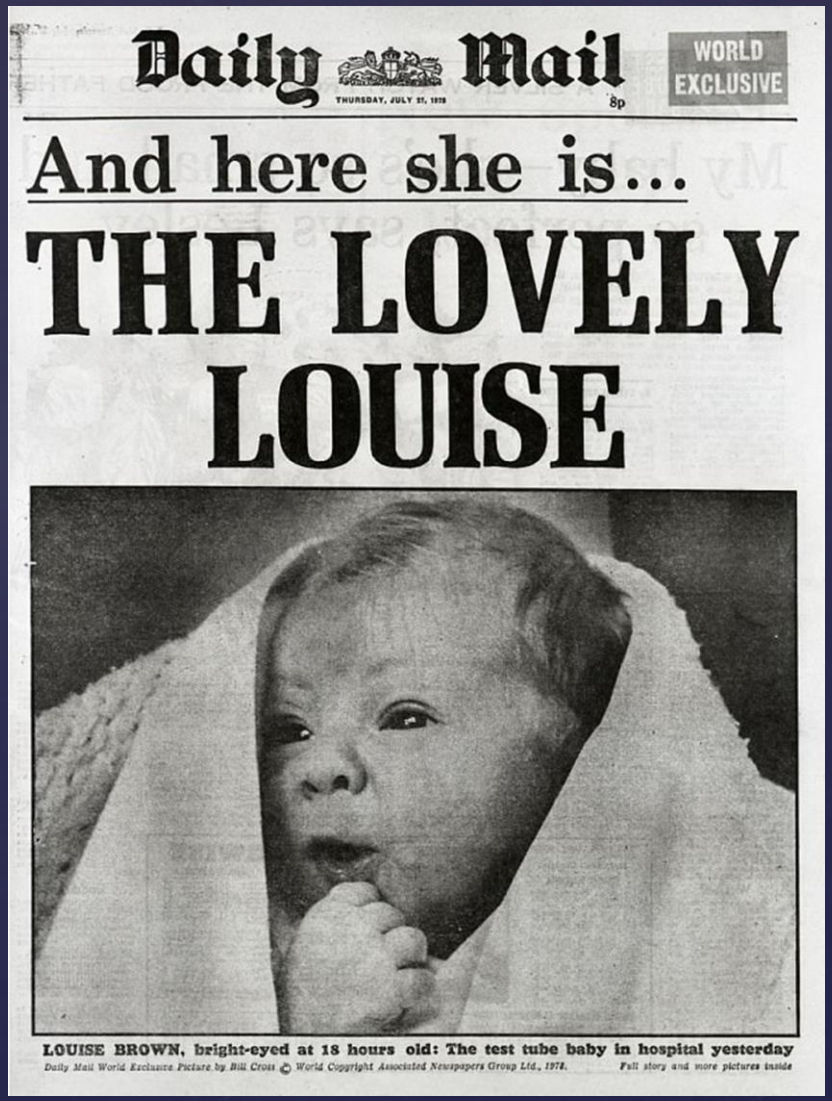

High-income countries
17.8%
Low- and middle-income countries
16.5%
Estimated lifetime prevalence of infertility

Ηλικία και γονιμότητα



❖25/07/1978

Το πρώτο παιδί μετά από λαπαροσκοπική λήψη ενός μόνο ωαρίου σε φυσιολογικό κύκλο γεννιέται στην Αγγλία από τους Steptoe και Edwards.



Daily Mail

THURSDAY, JULY 27, 1978

8p

WORLD EXCLUSIVE

And here she is...

THE LOVELY LOUISE

LOUISE BROWN, bright-eyed at 18 hours old: The test tube baby in hospital yesterday

Daily Mail World Exclusive Picture by Bill Cross © World Copyright Associated Newspapers Group Ltd., 1978.

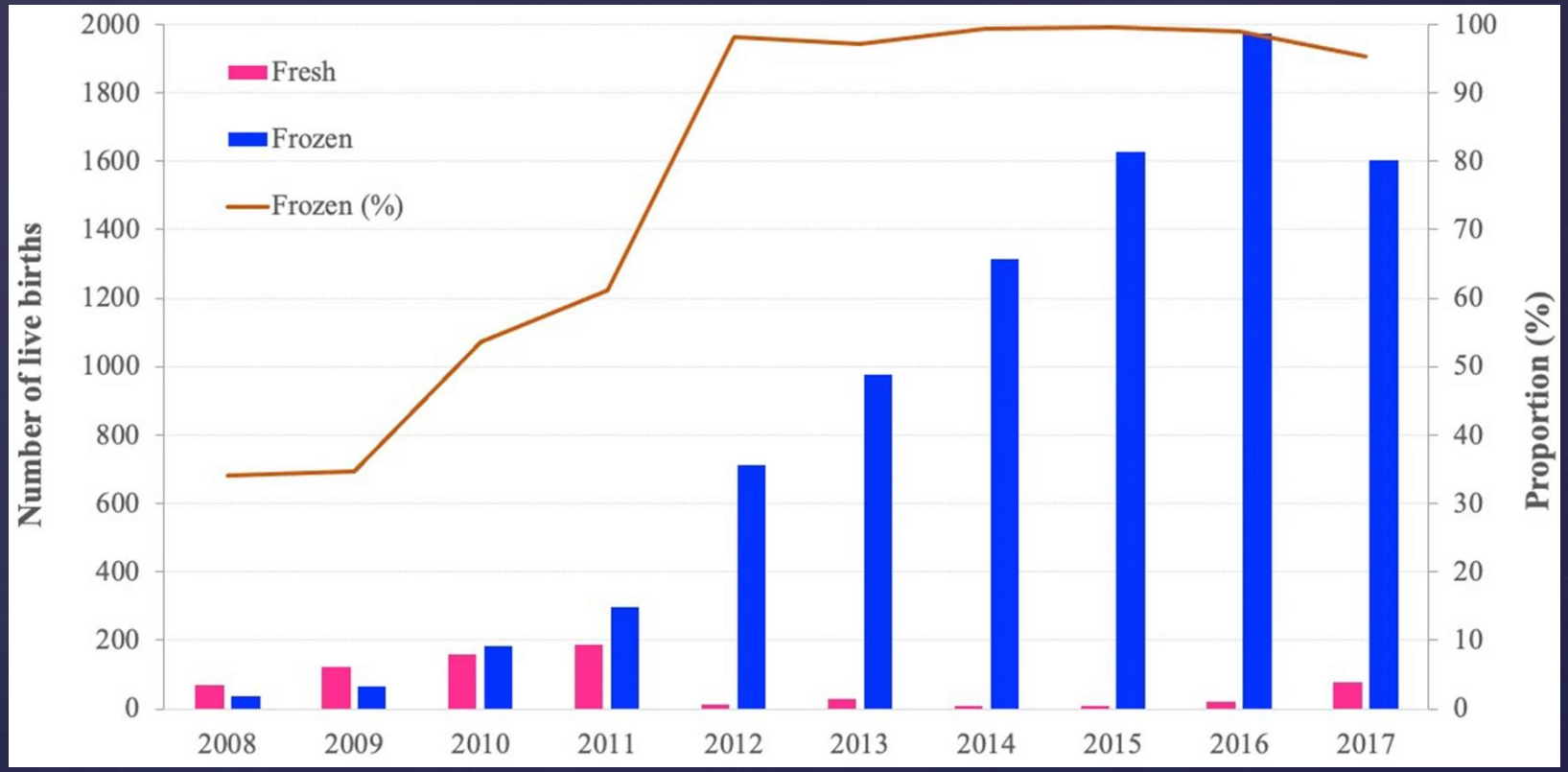
Full story and more pictures inside

Article | Open access | Published: 16 March 2022

Association of adverse birth outcomes with in vitro fertilization after controlling infertility factors based on a singleton live birth cohort

Huiting Yu, Zhou Liang, Renzhi Cai, Shan Jin, Tian Xia, Chunfang Wang & Yanping Kuang

Scientific Reports **12**, Article number: 4528 (2022) | Cite this article



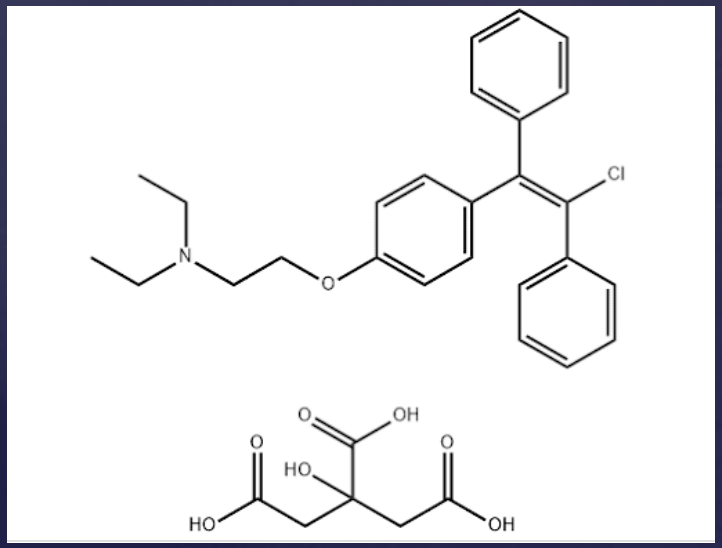
The trends of live births by fresh- and frozen-embryo transfer. From 2008 to 2017, there was increased in trend in the proportion of frozen-embryo transfer (Cochran–Armitage trend test $\chi^2 = 41.06$, $P < 0.0001$).

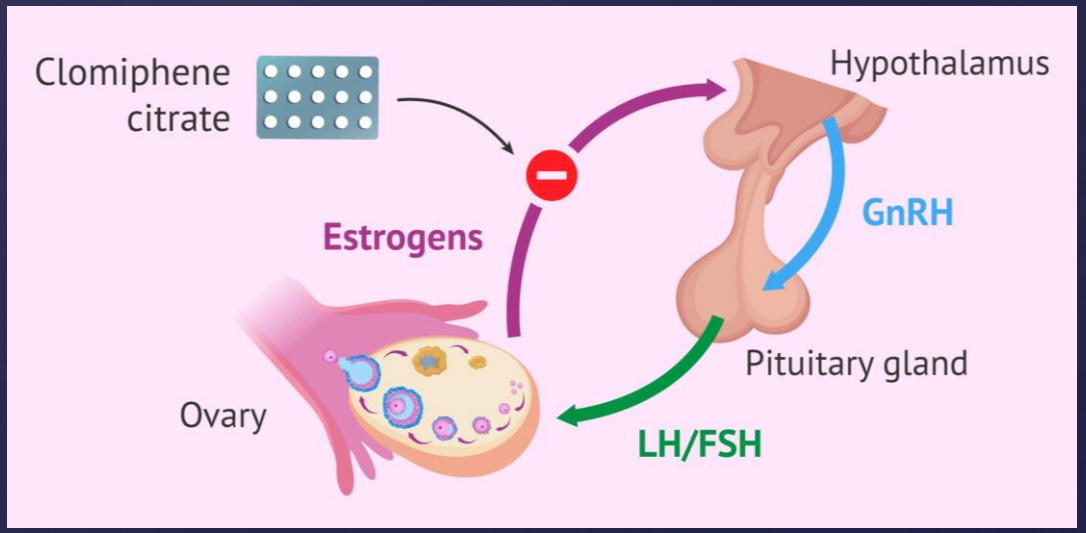
Φάρμακα γονιμότητας

- Τα πρωτόκολλα διέγερσης των ωοθηκών είναι αρκετά και θα πρέπει σε κάθε περίπτωση να επιλέγονται εξατομικευμένα, σύμφωνα με τις ιδιαιτερότητες κάθε γυναίκας, ως προς τα φάρμακα που θα χορηγηθούν, την έναρξη, την ημερήσια δοσολογία και τη διάρκεια χορήγησής τους.
- Διέγερση των ωοθηκών δύναται να λάβει χώρα και σε άλλες περιπτώσεις πέραν της εξωσωματικής γονιμοποίησης, όπως επί σπερματέγχυσης, αλλά και επί αραιομηνόρροιας/αμηνόρροιας, όπου η ωοθυλακιορρηξία απουσιάζει ή σπανίζει.
- Τα φάρμακα γονιμότητας που χρησιμοποιούνται είναι: η κιτρική κλομιφαίνη, οι αναστολείς αρωματάσης (κυρίως η λετροζόλη) και οι γοναδοτροπίνες, ενώ οι καρκίνοι που πιθανόν σχετίζονται με τη χρήση αυτών είναι ο καρκίνος των ωοθηκών, του ενδομητρίου και του μαστού.

Κιτρική κλομιφαίνη

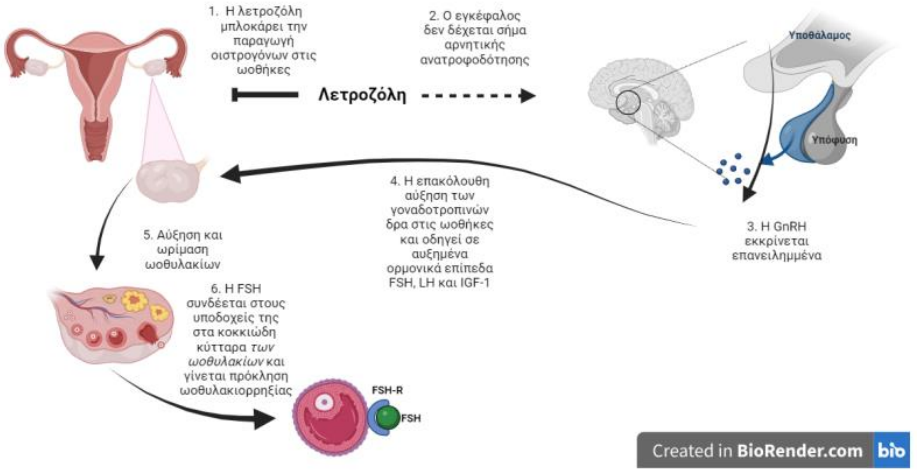
- Δρα στη μήτρα και στον κόλπο ως αντιοιστρογόνο και προσδένεται στους οιστρογονικούς υποδοχείς στον υποθάλαμο και στην υπόφυση.
- Αναστέλλεται ο αρνητικός μηχανισμός παλίνδρομης αλληλορύθμισης με αποτέλεσμα την αύξηση της έκκρισης της GnRH και κατ' επέκταση των γοναδοτροπινών από την υπόφυση.
- Χορηγείται για 5 ημέρες με έναρξη από την 2η ημέρα του κύκλου με δισκία από του στόματος και αρχική δόση 50 mg/ημέρα με σταδιακή αύξηση της δόσης επί μη απόκρισης, που δεν θα πρέπει να ξεπερνά τα 250 mg ημερησίως.
- Ανεπιθύμητες δράσεις: κεφαλαλγία, οπτικές διαταραχές και εξάψεις.





Αναστολείς αρωματάσης

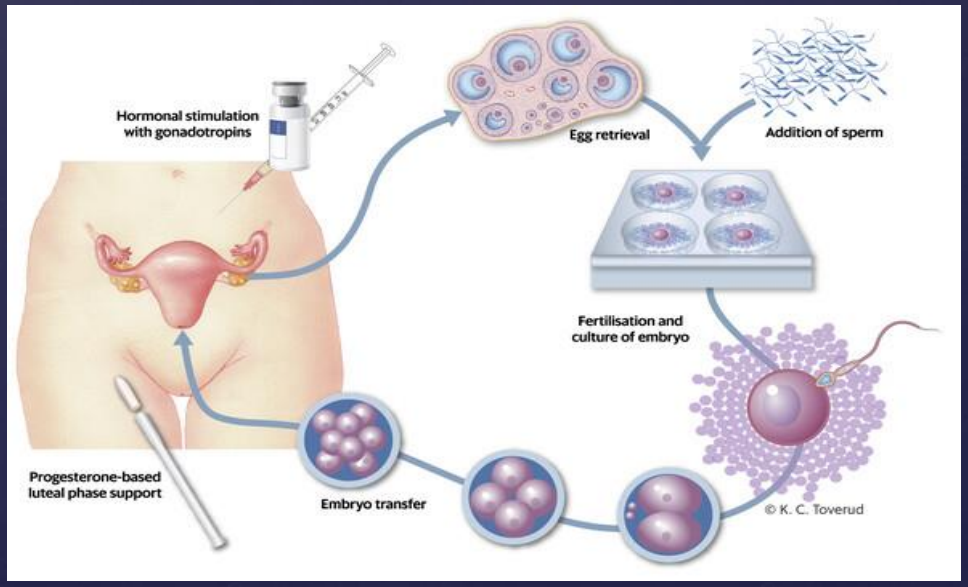
- Η δράση των αναστολέων αρωματάσης (λετροζόλη, αναστραζόλη) βασίζεται στην αναστολή μετατροπής των ανδρογόνων σε οιστρογόνα με αποτέλεσμα την αύξηση της FSH με την μείωση των οιστρογόνων μέσω του feedback και τη διέγερση των ωοθηκών.
- Πλεονεκτήματα:
- Τα παραγόμενα από το αναπτυσσόμενο ωοθυλάκιο οιστρογόνα, μέσω του feedback εμποδίζουν την υπέρμετρη έκκριση FSH (αφού οι υποδοχείς, σε αντίθεση με την κλομιφαίνη είναι ελεύθεροι), και έτσι προάγεται η ωοθυλακιορρηξία.
- Όχι δυσμενής επίδραση στο ενδομήτριο.



Εικόνα 4: Αποτελέσματα αναστολής βιοσύνθεσης οιστρογόνων από την λετροζόλη: Κεντρική δράση: (1) μετά την πρόσληψη λετροζόλης αναστέλλεται η παραγωγή οιστρογόνων στις ωοθήκες, (2) ο κεντρικός μηχανισμός αρνητικής ανάδρασης στον εγκέφαλο δεν επηρεάζεται και (3) ο υποθάλαμος συνεχίζει να εκκρίνει GnRH. (4) Η επακόλουθη αύξηση των γοναδοτροπινών δρα στις ωοθήκες και οδηγεί σε αυξημένα ορμονικά επίπεδα, με αποτέλεσμα (5) την ανάπτυξη και την ωρίμαση των ωοθυλακίων. (6) Η FSH συνδέεται στους υποδοχείς της στα κοκκιώδη κύτταρα των ωοθυλακίων και γίνεται πρόκληση ωοθυλακιορρηξίας (δημιουργία εικόνας μέσω www.BioRender.com).

Γοναδοτροπίνες

- ✓ Ωοθυλακιοτρόπος ορμόνη (FSH): διεγείρει την παραγωγή οιστρογόνων από τα ωοθυλάκια και σε συνδυασμό με αυτά προάγει την ωρίμανση των πρώιμων ωοθυλακίων σε ώριμα ωοθυλάκια.
- ✓ Ωχρινοτρόπος ορμόνη (LH): προάγει τη στεροειδογένεση και την ανάπτυξη του κυρίαρχου ωοθυλακίου και προκαλεί την ωορρηξία με μια απότομη αύξηση της τιμής της στα μέσα του εμμηνορρυσιακού κύκλου.
- ✓ Ανθρώπινη χοριακή γοναδοτροπίνη (hCG): χρησιμοποιείται για την προώθηση του τελικού σταδίου ωρίμανσης του ωοθυλακίου και την εξέλιξη του ανώριμου ωοκυττάρου από την πρόφαση Ι μέσω της μειωτικής διαίρεσης στη μεταφάση ΙΙ.
- ✓ Εκλυτική ορμόνη των γοναδοτροπινών (GnRH): διεγείρει την έκκριση γοναδοτροπινών.



Οι κυριότεροι αγωνιστές της GnRH είναι:

- ✓ η λευπρολίδη (leuprolide)
- ✓ η μπουσερελίνη (buserelin)
- ✓ η τριπτορελίνη (triptorelin)
- ✓ η ναφαρελίνη (nafarelin)
- ✓ η γοσερελίνη (goserelin)
- ✓ η ιστρελίνη (histrelin)
- ✓ η δεσλορελίνη (deslorelin)

Καρκίνος ωοθηκών

- 4η αιτία θανάτου στις γυναίκες (γενικά) και η συχνότερη αιτία θανάτου από γυναικολογικό καρκίνο.
- Ο κίνδυνος μιας γυναίκας να νοσήσει από καρκίνο των ωοθηκών κατά τη διάρκεια της ζωής της είναι περίπου 1 προς 87.
- Η πιθανότητα θανάτου από καρκίνο των ωοθηκών κατά τη διάρκεια της ζωής της είναι περίπου 1 προς 130. (Αυτές οι στατιστικές δεν υπολογίζουν τους χαμηλής κακοήθειας δυνητικούς όγκους των ωοθηκών). *American Cancer Society 2024*
- Παράγοντες κινδύνου: οικογενειακό ιστορικό Ca ωοθηκών ή του μαστού, αυξημένη ηλικία, ατοκία, πυελική φλεγμονώδης νόσος, υπογονιμότητα, μεταλλάξεις BRCA1 και BRCA2, παχυσαρκία, δίαιτα πλούσια σε λίπη, κάπνισμα, έλλειψη σωματικής δραστηριότητας.
- Προστατευτικοί παράγοντες: θηλασμός, ΑΟΔ, πολυτοκία, βιταμίνη D.

Φάρμακα γονιμότητας και καρκίνος ωοθηκών

- ✓ Δύο θεωρίες

Θεωρία «αδιάκοπης ωορρηξίας»

Θεωρία των «αυξημένων επιπέδων γοναδοτροπίνης»

Portrait of Dora Maar by Pablo Picasso (1937)

- *Fathalla MF. Incessant ovulation–a factor in ovarian neoplasia? Lancet. (1971) 2:163. 10.1016/S0140-6736(71)92335-X*

Meta-Analysis > Am J Epidemiol. 1992 Nov 15;136(10):1184-203.
doi: 10.1093/oxfordjournals.aje.a116427.

Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group

A S Whittemore [1], R Harris, J Itnyre

Abstract

Data collected from 2,197 white ovarian cancer patients and 8,893 white controls in 12 US case-control studies conducted in the period 1956-1986 were used to evaluate the relation of invasive epithelial ovarian cancer to reproductive and menstrual characteristics, exogenous estrogen use, and prior pelvic surgeries. Clear trends of decreasing risk were evident with increasing number of pregnancies (regardless of outcome) and increasing duration of breast feeding and oral contraceptive use. Ovarian dysfunction leading to both infertility and malignancy is an unlikely explanation for these trends for several reasons: 1) The trends were evident even among the highly parous; 2) risk among nulliparous women did not vary by marital status or gravidity; and 3) risk among ever-married women showed little relation to length of longest pregnancy attempt or history of clinically diagnosed infertility. Risk was increased among women who had used fertility drugs and among women with long total duration of premenopausal sexual activity without birth control; these associations were particularly strong among the nulligravid. No consistent trends in risk were seen with age at menarche, age at menopause, or duration of estrogen replacement therapy. A history of tubal ligation or of hysterectomy with ovarian conservation was associated with reduced ovarian cancer risk. These observations suggest that pregnancy, breast feeding, and oral contraceptive use induce biological changes that protect against ovarian malignancy, that, at most, a small fraction of the excess ovarian cancer risk among nulliparous women is due to infertility, and that any increased risk associated with infertility may be due to the use of fertility drugs.

Comparative Study > N Engl J Med. 1994 Sep 22;331(12):771-6.
doi: 10.1056/NEJM199409223311204.

Ovarian tumors in a cohort of infertile women

M A Rossing [1], J R Daling, N S Weiss, D E Moore, S G Self

Affiliations + expand

PMID: 8065405 DOI: 10.1056/NEJM199409223311204

RESULTS

There were 11 invasive or borderline malignant ovarian tumors, as compared with an expected number of 4.4 (standardized incidence ratio, 2.5; 95 percent confidence interval, 1.3 to 4.5). Nine of the women in whom ovarian tumors developed had taken clomiphene; the adjusted relative risk among these women, as compared with that among infertile women who had not taken this drug, was 2.3 (95 percent confidence interval, 0.5 to 11.4). Five of the nine women had taken the drug during 12 or more monthly cycles. This period of treatment was associated with an increased risk of ovarian tumors among both women with ovarian abnormalities and those without apparent abnormalities (relative risk, 11.1; 95 percent confidence interval, 1.5 to 82.3), whereas treatment with the drug for less than one year was not associated with an increased risk.

CONCLUSIONS

Prolonged use of clomiphene may increase the risk of a borderline or invasive ovarian tumor.

American Journal of Epidemiology

Vol. 147, No. 11
Printed in U.S.A.

A BRIEF ORIGINAL CONTRIBUTION

Cancer Incidence in a Cohort of Infertile Women

Baruch Modan,[1,2] Elaine Ron,[3] Liat Lerner-Geva,[1] Tzvia Blumstein,[1] Joseph Menczer,[4] Jaron Rabinovici,[5] Gabriel Oelsner,[5] Laurence Freedman,[1] Shlomo Mashiach,[5] and Bruno Lunenfeld[6]

Among 2,496 infertile Israeli women treated between 1964 and 1974, 143 cancer cases were observed as compared with 116.1 expected (standardized incidence ratio (SIR) = 1.2, 95% confidence interval (CI) 1.0–1.5) through 1991. Site-specific analysis revealed 12 ovarian cancers versus 7.2 expected (SIR = 1.6, 95% CI 0.8–2.9), 21 endometrial cancers versus 4.3 expected (SIR = 4.85, 95% CI 3.0–7.4), and 59 breast cancers versus 46.6 expected (SIR = 1.3, 95% CI 0.96–1.6). Sensitivity analysis revealed that confounding was unlikely to explain the raised risk of endometrial cancer, but nulliparity might explain the increased risk of ovarian cancer. The excess of endometrial cancer was prominent among patients with normal estrogen production but progesterone deficiency (SIR = 9.4, 95% CI 5.0–16.0). The risk for ovarian cancer was similar among the total groups of treated and untreated patients (SIR = 1.7 vs. 1.6). The standardized incidence ratio for endometrial cancer was higher among the treated group than the untreated group, although not significantly. Treatment with ovulation-inducing drugs does not appear to increase the risk for ovarian cancer, but its role cannot be completely excluded. *Am J Epidemiol* 1998;147:1038–42.

breast neoplasms; endometrial neoplasms; infertility; ovarian neoplasms; ovulation induction

Human Reproduction Vol.17, No.8 pp. 2209–2213, 2002

Cancer incidence following treatment for infertility at a clinic in the UK

Pat Doyle[1,5], Noreen Maconochie[1], Valerie Beral[2], Anthony J.Swerdlow[3] and S.L.Tan[4]

[1]Epidemiology Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, University of London, Keppel St, London WC1E 7HT, [2]Imperial Cancer Research Fund, University of Oxford, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, [3]Section of Epidemiology, Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK and [4]Department of Obstetrics and Gynaecology, McGill University, Royal Victoria Hospital, Montreal, Canada

[5]To whom correspondence should be addressed. E-mail: pat.doyle@lshtm.ac.uk

BACKGROUND: There is concern about the long-term health impact of ovarian stimulation treatment for infertility, in particular the effect on cancer risk. The aim of this study was to investigate the incidence of cancer in a cohort of women attending a large infertility clinic in the UK. METHODS: Women who were UK residents attending the clinic between January 1, 1975 and December 31, 1989 were identified for the study. The cohort was followed-up and cancer incidence rates calculated. RESULTS: The study cohort was made up of 5556 women of whom 75% had received ovarian stimulation drug treatment at the clinic. A total of 118 cancers (including 55 breast, four corpus uteri and six ovarian) were incident in the cohort from the beginning of 1990 to the end of 1997. The incidence rates of cancer of the breast, corpus uteri and ovary were not significantly different from expectation based on national cancer rates, and were similar for women who had received hormonal treatment to stimulate their ovaries and those who had not. CONCLUSIONS: These data do not support a hypothesis linking infertility treatment involving ovarian stimulation with increased breast, uterine and ovarian cancer over the follow-up period studied.

› Obstet Gynecol. 2004 Jun;103(6):1194-203. doi: 10.1097/01.AOG.0000128139.92313.74.

Ovarian cancer risk after the use of ovulation-stimulating drugs

Louise A Brinton [1], Emmet J Lamb, Kamran S Moghissi, Bert Scoccia, Michelle D Althuis, Jerome E Mabie, Carolyn L Westhoff

Affiliations + expand

PMID: 15172852 DOI: 10.1097/01.AOG.0000128139.92313.74

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.

FERTILITY AND STERILITY®
Vol. 67, No. 6, June 1997

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Published by Elsevier Science Inc.

Infertility, fertility drugs, and invasive ovarian cancer: a case-control study*

Berit Jul Mosgaard, M.D.†‡
Øjvind Lidegaard, M.D.†
Susanne Krüger Kjaer, M.D.§
Geert Schou, M.Sc.§
Anders Nyboe Andersen, M.D.‖

Herlev Hospital and Rigshospitalet, University of Copenhagen, and Danish Cancer Society, Copenhagen, Denmark

Objective: To assess the risk of invasive ovarian cancer among infertile women treated with fertility drugs.

Design: A case-control study.

Setting: Nationwide data based on public registers.

Patient(s): All Danish women (below the age of 60 years) with ovarian cancer during the period from 1989 to 1994 and twice the number of age-matched population controls. Included in the analysis were 684 cases and 1,721 controls.

Main Outcome Measure(s): Influence of parity, infertility, and fertility drugs on the risk of ovarian cancer after multivariate confounder control. Risk measure(s): odds ratios (OR) with 95% confidence intervals.

Result(s): Nulliparous women had an increased risk of ovarian cancer compared with parous women: OR 1.5 to 2.0. Infertile, nontreated nulliparous women had an OR of 2.7 (1.3 to 5.5) compared with noninfertile nulliparous women. The OR of ovarian cancer among treated nulliparous women was 0.8 (0.4 to 2.0) and among treated parous 0.6 (0.2 to 1.3), compared with nontreated nulliparous and parous infertile women, respectively.

Conclusion(s): Nulliparity implies a 1.5- to 2-fold increased risk of ovarian cancer. Infertility without medical treatment among these women increased the risk further. Among parous as well as nulliparous women, treatment with fertility drugs did not increase the ovarian cancer risk compared with nontreated infertile women. (Fertil Steril® 1997;67:1005–12. © 1997 by American Society for Reproductive Medicine.)

BMJ

RESEARCH

Use of fertility drugs and risk of ovarian cancer: Danish population based cohort study

Allan Jensen, assistant professor of cancer epidemiology,[1] Heidi Sharif, specialist in obstetrics and gynaecology,[1] Kirsten Frederiksen, associate professor of medical statistics,[1] Susanne Krüger Kjær, professor of cancer epidemiology[1,2]

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[2]The Juliane Marie Center, Copenhagen University Hospital,

Correspondence to: A Jensen
allan@cancer.dk

Cite this as: *BMJ* 2009;338:b249
doi:10.1136/bmj.b249

ABSTRACT

Objective To examine the effects of fertility drugs on overall risk of ovarian cancer using data from a large cohort of infertile women.

Design Population based cohort study.

Setting Danish hospitals and private fertility clinics.

Participants 54 362 women with infertility problems referred to all Danish fertility clinics during 1963-98. The median age at first evaluation of infertility was 30 years (range 16-55 years), and the median age at the end of follow-up was 47 (range 18-81) years. Included in the analysis were 156 women with invasive epithelial ovarian cancer (cases) and 1241 subcohort members identified in the cohort during follow-up in 2006.

Main outcome measure Effect of four groups of fertility drugs (gonadotrophins, clomifene citrate, human chorionic gonadotrophin, and gonadotrophin releasing hormone) on overall risk of ovarian cancer after adjustment for potential confounding factors.

Results Analyses within cohort showed no overall increased risk of ovarian cancer after any use of gonadotrophins (rate ratio 0.83, 95% confidence interval 0.50 to 1.37), clomifene (1.14, 0.79 to 1.64), human chorionic gonadotrophin (0.89, 0.62 to 1.29), or gonadotrophin releasing hormone (0.80, 0.42 to 1.51). Furthermore, no associations were found between all four groups of fertility drugs and number of cycles of use, length of follow-up, or parity.

Conclusion No convincing association was found between use of fertility drugs and risk of ovarian cancer.

Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden

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Objective: To study the association between hormonal infertility treatment and ovarian neoplasia.
Design: Historical cohort study.
Setting: Three university hospitals in Sweden.
Patient(s): A total of 2,768 women assessed and treated for infertility and infertility-associated disorders between 1961 and 1975.
Intervention(s): Exposed women received clomiphene citrate and/or gonadotropins.
Main Outcome Measure(s): Incidence of ovarian neoplasia.
Result(s): No overall excess risk of invasive ovarian cancer emerged compared with the general population. In women with gonadotropin treatment for non-ovulatory disorders, the risk was elevated (standardized incidence ratio [SIR] = 5.89; 95% confidence interval [CI] 1.91–13.75); four of the five cases reported hCG treatment only, rendering the biological plausibility uncertain. Multivariate analysis within the cohort indicated that treatment with gonadotropins only was associated with an increased risk of invasive cancer (relative risk = 5.28; 95% CI 1.70–16.47). For borderline tumors, a more than threefold overall increase of tumors (SIR = 3.61; 95% CI 1.45–7.44) was noted; women exposed to clomiphene because of ovulatory disorders showed the highest risk (SIR = 7.47; 95% CI 1.54–21.83).
Conclusion(s): Our findings of increased risk of ovarian cancer after gonadotropins and of borderline tumors after clomiphene treatment need to be interpreted with caution. However, concern is raised, and further research on the long-term safety particularly of modern hormonal infertility treatment in IVF programs is warranted. (Fertil Steril® 2009;91:1152–8. ©2009 by American Society for Reproductive Medicine.)

Key Words: Ovarian neoplasia risk, hormonal infertility treatment, ovulatory disorders, historical cohort

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case–Control Study

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Abstract

Background: Previous studies examining associations between use of fertility drugs and ovarian cancer risk have provided conflicting results. We used data from a large case–control study to determine whether fertility drug use significantly impacts ovarian cancer risk when taking into account parity, gravidity, and cause of infertility.

Methods: Data from the Hormones and Ovarian Cancer Prediction (HOPE) study were used (902 cases, 1,802 controls). Medical and reproductive histories were collected via in-person interviews. Logistic regression was used to calculate ORs and 95% confidence intervals (CI). Models were adjusted for age, race, education, age at menarche, parity, oral contraceptive use, breastfeeding, talc use, tubal ligation, and family history of breast/ovarian cancer.

Results: Ever use of fertility drugs was not significantly associated with ovarian cancer within the total HOPE population (OR, 0.93; 95% CI, 0.65–1.35) or among women who reported seeking medical attention for infertility (OR, 0.87; 95% CI, 0.54–1.40). We did observe a statistically significant increased risk of ovarian cancer for ever use of fertility drugs among women who, despite seeking medical attention for problems getting pregnant, remained nulligravid (OR, 3.13; 95% CI, 1.01–9.67).

Conclusions: These results provide further evidence that fertility drug use does not significantly contribute to ovarian cancer risk among the majority of women; however, women who despite infertility evaluation and fertility drug use remain nulligravid, may have an elevated risk for ovarian cancer.

Impact: Our results suggest that fertility drug use does not significantly contribute to overall risk of ovarian cancer when adjusting for known confounding factors. *Cancer Epidemiol Biomarkers Prev; 21(8); 1282–92. ©2012 AACR.*

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Fertility Drug Use and the Risk of Ovarian Tumors in Infertile Women: A Case-Control Study

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Abstract

Objective—To assess the influence of infertility and fertility drugs on risk of ovarian tumors.

Design—Case-control study (Mayo Clinic Ovarian Cancer Study).

Setting—Ongoing academic study of ovarian cancer.

Patient(s)—A total of 1900 women (1028 with ovarian tumors and 872 controls, frequency matched on age and region of residence) who had provided complete information in a self-report questionnaire about history of infertility and fertility drug use.

Intervention(s)—None

Main outcome measure(s)—Effect of infertility history, use of fertility drugs and oral contraception and gravidity on the risk of ovarian tumor development, after controlling for potential confounders.

Result(s)—Among women who had a history of infertility, use of fertility drugs was reported by 24% (44/182) of controls and 17% (38/226) of cases. Infertile women who used fertility drugs were not at increased risk of developing ovarian tumors compared to infertile women who did not use fertility drugs, adjusted odds ratio was 0.64 (95% CI 0.37, 1.11). Findings were similar when stratified by gravidity and when analyzed separately for borderline versus invasive tumors.

Conclusion(s)—We did not find any significant association between fertility drug use and risk of ovarian tumors. Further larger, prospective studies are needed to confirm this observation.

Review > Cochrane Database Syst Rev. 2013 Aug 13;2013(8):CD008215.
doi: 10.1002/14651858.CD008215.pub2.

Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility

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Affiliations + expand

PMID: 23943232 PMCID: PMC6457641 DOI: 10.1002/14651858.CD008215.pub2

Main results

We included 11 case-control studies and 14 cohort studies, which included a total of 182,972 women.

Seven cohort studies showed no evidence of an increased risk of invasive ovarian cancer in subfertile women treated with any drug compared with untreated subfertile women. Seven case-control studies showed no evidence of an increased risk, compared with control women of a similar age. Two cohort studies reported an increased incidence of invasive ovarian cancer in subfertile women treated with any fertility drug compared with the general population. One of these reported a SIR of 5.0 (95% confidence interval (CI) 1.0 to 15), based on three cancer cases, and a decreased risk when cancer cases diagnosed within one year of treatment were excluded from the analysis(SIR 1.67, 95% CI 0.02 to 9.27). The other cohort study reported an OR of 2.09 (95% CI 1.39 to 3.12), based on 26 cases.

For borderline ovarian tumours, exposure to any fertility drug was associated with a two to three-fold increased risk in two case-control studies. One case-control study reported an OR of 28 (95% CI 1.5 to 516), which was based on only four cases. In one cohort study, there was more than a two-fold increase in the incidence of borderline tumours compared with the general population (SIR 2.6, 95% CI 1.4 to 4.6) and in another the risk of a borderline ovarian tumour was HR 4.23 (95% CI 1.25 to 14.33) for subfertile women treated with in vitro fertilisation (IVF) compared with a non-IVF treated group with more than one year of follow-up.

There was no evidence of an increased risk in women exposed to clomiphene alone or clomiphene plus gonadotrophin, compared with unexposed women. One case-control study reported an increased risk in users of human menopausal gonadotrophin (HMG)(OR 9.4, 95% CI 1.7 to 52). However, this estimate is based on only six cases with a history of HMG use.

Authors' conclusions

We found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. There may be an increased risk of borderline ovarian tumours in subfertile women treated with IVF. Studies showing an increase in the risk of ovarian cancer had a high overall risk of bias, due to retrospective study design, lack of accounting for potential confounding and estimates based on a small number of cases. More studies at low risk of bias are needed.

Lancet. 1999 Nov 6;354(9190):1586-90. doi: 10.1016/S0140-6736(99)05203-4.

Risk of cancer after use of fertility drugs with in-vitro fertilisation

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Affiliations + expand

PMID: 10560672 DOI: 10.1016/S0140-6736(99)05203-4

Method: Ten Australian IVF clinics provided data for women who had been referred for IVF before Jan 1, 1994. The frequencies of invasive breast, ovarian, and uterine cancer were assessed by record linkage to population-based cancer registries and the national death index. The observed number of cancers was compared with the expected number calculated by application of age-standardised general-population cancer rates to the cohort. Standardised incidence ratios (SIRs) were derived from the ratio of observed to expected cases.

Findings: The cohort consisted of 29,700 women: 20,656 were exposed to fertility drugs and 9044 were not. 143 breast cancers, 13 ovarian cancers, and 12 cancers of the uterus occurred among these women. For breast and ovarian cancer the incidence was no greater than expected (SIR 0.91 [95% CI 0.74-1.13] for breast cancer and 0.88 [0.42-1.84] for ovarian cancer in the exposed group and 0.95 [0.73-1.23] for breast cancer and 1.16 [0.52-2.59] for ovarian cancer in the unexposed group). The incidence of uterine cancer was no higher than expected in the exposed group (1.09 [0.45-2.61]) but was significantly higher in the unexposed group (2.47 [1.18-5.18]). Women with unexplained infertility had significantly more cancers of the ovary and uterus than expected (2.64 [1.10-6.35] and 4.59 [1.91-11.0], whole cohort). Analysis of cancer incidence within 12 months of exposure to fertility drugs with IVF showed that incidence was significantly higher than expected for breast and uterine cancer (1.96 [1.22-3.15] and 4.96 [1.24-19.8]).

Interpretation: Women who have been exposed to fertility drugs with IVF seem to have a transient increase in the risk of having breast or uterine cancer diagnosed in the first year after treatment, though the incidence overall is no greater than expected. Unexplained infertility was associated with an increased risk of a diagnosis of ovarian or uterine cancer.

Int J Gynecol Cancer. 2003 Jan-Feb;13(1):23-7. doi: 10.1136/ijgc-00009577-200301000-00004.

The possible association between in vitro fertilization treatments and cancer development

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PMID: 12631215 DOI: 10.1136/ijgc-00009577-200301000-00004

Abstract

The objective of this paper is to assess whether ovarian hyperstimulation and in vitro fertilization (IVF) are associated with increased risk of cancer development, using an historical cohort analysis of infertile women who attended the IVF unit, Lis Maternity Hospital Tel Aviv Medical Center, Tel Aviv, Israel. One thousand and 82 women participated in the IVF treatment program between 1984 and 1992. Cancer incidence rates were determined through the National Cancer Registry and were compared to the expected rates with respect to appropriate age and continent of birth. Twenty-one cases of cancer were observed as compared to 11 that were expected (SIR 1.91; 95% CI 1.18-2.91). When cancer cases that were diagnosed within one year of the IVF treatment were excluded from the analysis (SIR = 1.46; 95% CI 0.83-2.36), no significant excess risk of cancer was noted. We conclude that in this cohort of infertile women, the higher than expected cancer rate could not be attributed to IVF treatments. Special attention should be made to women who may be diagnosed with cancer during or shortly after IVF treatment.

Hum Reprod. 2011 Jan;26(1):253-8. doi: 10.1093/humrep/deq307. Epub 2010 Nov 18.

Malignancies among women who gave birth after in vitro fertilization

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Affiliations + expand

PMID: 21088017 DOI: 10.1093/humrep/deq307

Abstract

Background: Relatively few studies published to date have investigated IVF and cancer risk. In this study we compared the occurrence of cancer in women who gave birth after IVF with all other women who gave birth in the study period.

Methods: All women who were treated with IVF and gave birth during the years 1982-2006 in Sweden were identified from all IVF clinics, and the occurrence of cancer in these women was identified by linkage with the nationwide Swedish cancer register. Comparison was made with Mantel-Haenszel odds ratios (ORs), adjusting for year of delivery and maternal age, parity and smoking. Cancer before IVF was only studied in first parity women. Specific cancer forms were also studied.

Results: Among 24058 women who had been treated with IVF, 1279 appeared in the cancer register. The total number of women studied in the population was 1 394 061, and 95 775 of these were registered in the cancer register. The risk for cancer before IVF was increased [OR 1.37, 95% confidence interval (CI) 1.27-1.48] and was especially high for ovarian cancer (3.93). The risk for cancer after IVF was significantly lower (OR 0.74, 95% CI 0.67-0.82), mainly due to a lower than expected risk for breast and cervical cancer. The risk for ovarian cancer was increased but lower than the risk before IVF (2.13).

Conclusions: Cancer or cancer treatment may increase the risk for infertility leading to IVF. After IVF, in most cases with treatment with fertility hormones, a significantly low cancer risk was found. Ovarian cancer showed an increased risk, although lower than before IVF. One possible reason is ovarian pathology causing both infertility and an increased cancer risk.

Human Reproduction, Vol.26, No.12 pp. 3456–3465, 2011
Advanced Access publication on October 26, 2011 doi:10.1093/humrep/der322

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of borderline and invasive ovarian tumours after ovarian stimulation for *in vitro* fertilization in a large Dutch cohort

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BACKGROUND: Long-term effects of ovarian stimulation for IVF on the risk of ovarian malignancies are unknown.

METHODS: We identified a nationwide historic cohort of 19 146 women who received IVF treatment in the Netherlands between 1983 and 1995, and a comparison group of 6006 subfertile women not treated with IVF. In 1997–1999, data on reproductive risk factors were obtained from 65% of women and data on subfertility (treatment) were obtained from the medical records. The incidence of ovarian malignancies (including borderline ovarian tumours) through 2007 was assessed through linkage with disease registries. The risk of ovarian malignancies in the IVF group was compared with risks in the general population and the subfertile comparison group.

RESULTS: After a median follow-up of 14.7 years, the risk of borderline ovarian tumours was increased in the IVF group compared with the general population [standardized incidence ratio (SIR) = 1.76; 95% confidence interval (CI) = 1.16–2.56]. The overall SIR for invasive ovarian cancer was not significantly elevated, but increased with longer follow-up after first IVF ($P = 0.02$); the SIR was 3.54 (95% CI = 1.62–6.72) after 15 years. The risks of borderline ovarian tumours and of all ovarian malignancies combined in the IVF group were significantly increased compared with risks in the subfertile comparison group (hazard ratios = 4.23; 95% CI = 1.25–14.33 and 2.14; 95% CI = 1.07–4.25, respectively, adjusted for age, parity and subfertility cause).

CONCLUSIONS: Ovarian stimulation for IVF may increase the risk of ovarian malignancies, especially borderline ovarian tumours. More large cohort studies are needed to confirm these findings and to examine the effect of IVF treatment characteristics.

Key words: ovarian stimulation / ovarian malignancies / fertility drugs / infertility / *in vitro* fertilization

Review > Int J Gynecol Cancer. 2013 Jan;23(1):16-24. doi: 10.1097/IGC.0b013e318277608b.

Meta-analysis on the possible association between in vitro fertilization and cancer risk

Li Li Li [1], Jun Zhou, Xia Jing Qian, Yi Ding Chen

Abstract

Objective: We aimed to examine the association between in vitro fertilization (IVF) and risk of cancers through conducting a meta-analysis of cohort studies.

Methods: Relevant studies were identified by using PubMed, ISI Web of knowledge, and Scopus through March 2012. Reference lists from retrieved articles were also reviewed. We included historical cohort studies that reported relative risks (RRs) with 95% confidence intervals (CIs) for the association between IVF and cancer risk. Both fixed- and random-effects models were used to calculate the summary risk estimates.

Results: Eight cohort studies involving 746,455 participants were included in this meta-analysis. The overall combined RRs for women with IVF treatment were 0.99 (95% CI, 0.74-1.32) for all-site cancer, 1.59 (95% CI, 1.24-2.03) for ovarian cancer, 0.89 (95% CI, 0.79-1.01) for breast cancer, and 1.07 (95% CI, 0.45-2.55) for cervical cancer. A beneficial effect was shown in the subgroup of breast cancer meta-analysis compared with women who gave birth (RR, 0.79; 95% CI, 0.65-0.95). Excess risk of ovarian cancer was still observed when analyses were restricted to studies with less than 8 years of follow-up (RR, 2.35; 95% CI, 1.03-5.37) and studies including cancer cases diagnosed within 1 year of the IVF treatment (RR, 1.71; 95% CI, 1.22-2.40). No evidence of substantial publication bias was observed.

Conclusions: This meta-analysis suggests that there is no significant association between IVF and cancer risk. A possible beneficial effect was shown in the subgroup of breast cancer meta-analysis. Excess risk of ovarian cancer was observed in the analysis of all the studies and subgroups. Special attention should be made to women who may be diagnosed with cancer during or shortly after IVF treatment. Studies of high methodological quality with larger population and longer follow-up are required to provide more evidences for a better understanding of the association.

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In Vitro Fertilization and Risk of Breast and Gynecologic Cancers: A Retrospective Cohort Study within the Israeli Maccabi Healthcare Services

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Abstract

Objective—To assess long-term cancer risks associated with *in vitro* fertilization (IVF).

Design—Record-linkage study

Setting—Health maintenance organization in Israel

Patients—87,403 women evaluated and/or treated for infertility on or after September 25, 1994 who were followed for cancer development through June 22, 2011: 522 breast, 41 endometrial, 45 ovarian, 311 *in situ* cervical and 32 invasive cervical cancers were identified.

Intervention(s)—None

Main Outcome Measures—Hazard ratios (HRs) for specific cancers

Results—We found no significant relationships of IVF exposures to the risks of breast, endometrial or ovarian cancers. Compared to women with no fertility treatment, the HR for ovarian cancer associated with IVF was 1.58 (95% CI 0.75–3.29), with higher risk among those receiving 4+ cycles (1.78, 95% CI 0.76–4.13). There was also a non-significantly elevated risk for endometrial cancer among women who received 1–3 IVF cycles (1.94, 0.73–5.12), but additional cycles were associated with lesser risk. In contrast, the risk of *in situ* cervical cancer was significantly reduced and invasive cervical cancer non-significantly reduced among women receiving IVF as well as other fertility treatments.

Conclusions—Our results regarding long-term effects were largely reassuring, but women receiving IVF should continue to be monitored given that the procedures involves potent ovulation stimulators and repeated ovarian punctures.

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Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk

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ABSTRACT

Objectives. To examine the risk of invasive epithelial ovarian cancer in a cohort of women seeking treatment for infertility.

Methods. Using whole-population linked hospital and registry data, we conducted a cohort study of 21,646 women commencing hospital investigation and treatment for infertility in Western Australia in the years 1982–2002. We examined the effects of IVF treatment, endometriosis and parity on risk of ovarian cancer and explored potential confounding by tubal ligation, hysterectomy and unilateral oophorectomy/salpingo-oophorectomy (USO).

Results. Parous women undergoing IVF had no observable increase in the rate of ovarian cancer (hazard ratio [HR] 1.01; 95% confidence interval [CI] 0.35–2.90); the HR in women who had IVF and remained nulliparous was 1.76 (95% CI 0.74–4.16). Women diagnosed with endometriosis who remained nulliparous had a three-fold increase in the rate of ovarian cancer (HR 3.11; 95% CI 1.13–8.57); the HR in parous women was 1.52 (95% CI 0.34–6.75). In separate analyses, women who had a USO without hysterectomy had a four-fold increase in the rate of ovarian cancer (HR 4.23; 95% CI 1.30–13.77). Hysterectomy with or without USO appeared protective.

Conclusions. There is no evidence of an increased risk of ovarian cancer following IVF in women who give birth. There is some uncertainty regarding the effect of IVF in women who remain nulliparous. Parous women diagnosed with endometriosis may have a slightly increased risk of ovarian cancer; nulliparous women have a marked increase in risk.

ORIGINAL ARTICLE: INFERTILITY

Treatment of infertility does not increase the risk of ovarian cancer among women with a *BRCA1* or *BRCA2* mutation

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Objective: To evaluate the relationship between use of fertility medication (i.e., selective estrogen receptor [ER] modulator, gonadotropin, or other) or infertility treatment (i.e., IVF or IUI) and the risk of ovarian cancer among women with a *BRCA1* or *BRCA2* mutation.
Design: A matched case-control study of 941 pairs of *BRCA1* or *BRCA2* mutation carriers with and without a diagnosis of ovarian cancer.
Setting: Genetic clinics.
Patient(s): Detailed information regarding treatment of infertility was collected from a routinely administered questionnaire.
Intervention(s): None.
Main Outcome Measure(s): Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals associated with fertility treatment.
Result(s): There was no significant relationship between the use of any fertility medication or IVF treatment (odds ratio, 0.66; 95% confidence interval 0.18–2.33) and the subsequent risk of ovarian cancer.
Conclusion(s): Our findings suggest that treatment for infertility does not significantly increase the risk of ovarian cancer among women with a *BRCA* mutation. (Fertil Steril® 2016;105:781–5. ©2016 by American Society for Reproductive Medicine.)
Key Words: *BRCA1*, *BRCA2*, infertility, in vitro fertilization, ovarian cancer

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Fertility treatments and invasive epithelial ovarian cancer risk in Jewish Israeli *BRCA1* or *BRCA2* mutation carriers

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Objective: To determine whether *BRCA* mutation carriers who undergo fertility treatments are at increased risk of developing invasive epithelial ovarian cancer (IEOC).
Design: Historical cohort study.
Setting: Tertiary university-affiliated medical center and the National Cancer Registry.
Patient(s): A total of 1,073 Jewish Israeli *BRCA* mutation carriers diagnosed in a single institution between 1995 and 2013, including 164 carriers (15.2%) who had fertility treatments that included clomiphene citrate (n = 82), gonadotropin (n = 69), in vitro fertilization (IVF) (n = 66), or a combination (n = 50), and 909 carriers not treated for infertility.
Intervention(s): None.
Main Outcome Measure(s): Odds ratios (OR) and 95% confidence intervals (CI) for IEOC association with fertility treatments and other hormone and reproductive variables.
Result(s): In 175 (16.3%) mutation carriers, IEOC was diagnosed; 139 women carried *BRCA1*, 33 carried *BRCA2*, and 3 had unknown mutations. Fertility treatments were not associated with IEOC risk (age-adjusted OR 0.63; 95% CI, 0.38–1.05) regardless of treatment type (with clomiphene citrate, OR 0.87; 95% CI, 0.46–1.63; with gonadotropin, OR 0.59; 95% CI, 0.26–1.31; with IVF, OR 1.08, 95% CI, 0.57–2.06). Multivariate analysis indicated an increased risk of IEOC with hormone-replacement therapy (OR 2.22; 95% CI, 1.33–3.69) and a reduced risk with oral contraceptives (OR 0.19; 95% CI, 0.13–0.28) in both *BRCA1* and *BRCA2* mutation carriers. Parity was a risk factor for IEOC by univariate but not multivariate analysis.
Conclusion(s): According to our results, treatments for infertile *BRCA* mutation carriers should not be contraindicated or viewed as risk modifiers for IEOC. Parity as a risk factor in *BRCA* mutation carriers warrants further investigation. (Fertil Steril® 2015;103:1305–12. ©2015 by American Society for Reproductive Medicine.)
Key Words: BRCA mutations, cancer risk, fertility treatment, ovarian cancer

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Cancer Risk in Women Treated with Fertility Drugs According to Parity status - A Registry-based Cohort Study

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Abstract

Background—Long-term safety of assisted reproductive techniques (ART) is of interest as use is increasing. Cancer risk is known to be affected by parity. This study examined risk of cancer after fertility treatment, stratified by women's parity.

Methods—Data was obtained on all women (n=1 353 724) born in Norway between 1960–1996. Drug exposure data (2004–2014) was obtained from the Norwegian Prescription Database [drugs used in ART and clomiphene citrate (CC)]. The Medical Birth Registry of Norway provided parity status. Hazard ratios were calculated for all site cancer, breast, cervical, endometrial, ovarian, colorectal, central nervous system, thyroid cancer and malignant melanoma.

Results—In 12 354 392 person-years of follow-up, 20 128 women were diagnosed with cancer. All-site cancer risk was (1.14, 1.03–1.26) and (1.10, 0.98–1.23) following CC and ART exposure respectively. For ovarian cancer, a stronger association was observed for both exposures in nulliparous (HR 2.49, 1.30–4.78, and HR 1.62, 0.78–3.35) versus parous women (HR 1.37, 0.64–2.96, and HR 0.87, 0.33–2.27).

Elevated risk of endometrial cancers was observed for CC exposure in nulliparous women (4.59, 2.68–7.84 vs. 1.44, 0.63–3.31). Risk was elevated for breast cancer in parous women exposed to CC (1.26, 1.03–1.54) and among nulliparous women after ART treatment (2.19, 1.08–4.44).

Conclusion—CC appears associated with increased risk of ovarian and endometrial cancer. Elevations in risks of breast and thyroid cancer were less consistent across type of drug exposure and parity.

Impact—Continued monitoring of fertility treatments is warranted.

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[Intervention Review]

Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility

Ivana Rizzuto[1], Renee F Behrens[2], Lesley A Smith[3]

ABSTRACT

Background

This is an updated version of the original Cochrane Review published in the Cochrane Library in 2013 (Issue 8) on the risk of ovarian cancer in women using infertility drugs when compared to the general population or to infertile women not treated. The link between fertility drugs and ovarian cancer remains controversial.

Objectives

To evaluate the risk of invasive ovarian cancer and borderline ovarian tumours in women treated with ovarian stimulating drugs for subfertility.

Search methods

The original review included published and unpublished observational studies from 1990 to February 2013. For this update, we extended the searches from February 2013 to November 2018; we evaluated the quality of the included studies and judged the certainty of evidence by using the GRADE approach. We have reported the results in a Summary of findings table to present effect sizes across all outcome types.

Selection criteria

In the original review and in this update, we searched for randomised controlled trials (RCTs) and non-randomised studies and case series including more than 30 participants.

Data collection and analysis

At least two review authors independently conducted eligibility and 'Risk of bias' assessments and extracted data. We grouped studies based on the fertility drug used for two outcomes: borderline ovarian tumours and invasive ovarian cancer. We conducted no meta-analyses due to expected methodological and clinical heterogeneity.

Main results

We included 13 case-control and 24 cohort studies (an additional nine new cohort and two case-control studies), which included a total of 4,684,724 women.

Two cohort studies reported an increased incidence of invasive ovarian cancer in exposed subfertile women compared with unexposed women. One reported a standardised incidence ratio (SIR) of 1.19 (95% confidence interval (CI) 0.54 to 2.25) based on 17 cancer cases. The other cohort study reported a hazard ratio (HR) of 1.93 (95% CI 1.18 to 3.18), and this risk was increased in women remaining nulligravid

› Fertil Steril. 2024 May 3:S0015-0282(24)00201-2. doi: 10.1016/j.fertnstert.2024.03.026. Online ahead of print.

Fertility drugs and cancer: a guideline

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Affiliations + expand

PMID: 38703170 DOI: 10.1016/j.fertnstert.2024.03.026

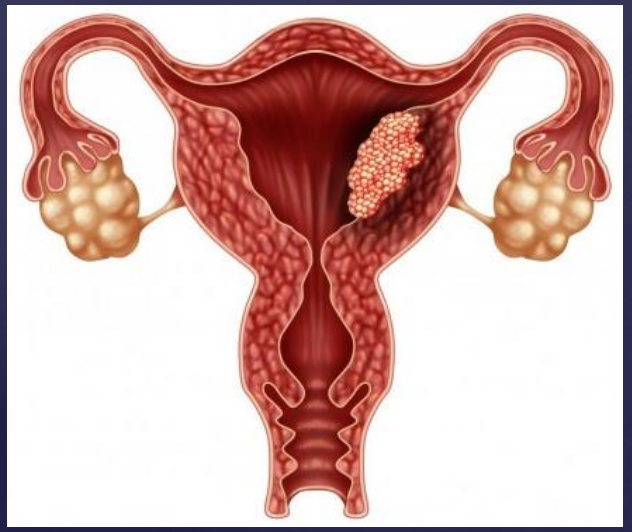
Abstract

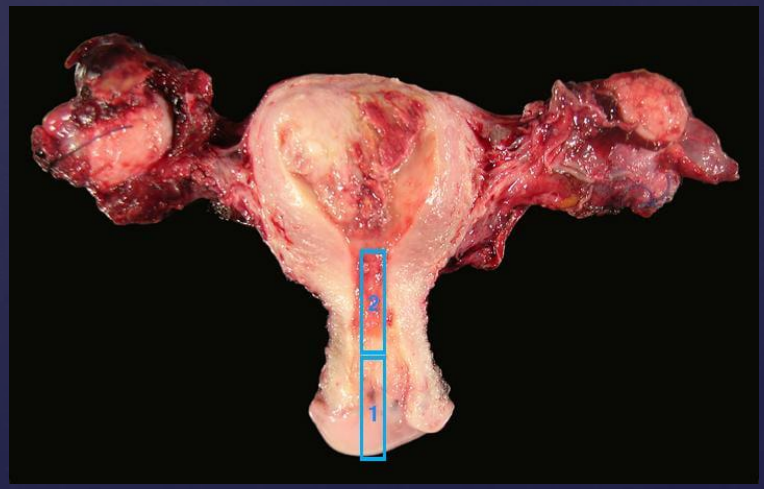
Methodological limitations in studying the association between the use of fertility drugs and cancer include the inherent increased risk of cancer in women who never conceive, the increased risk of cancer because of factors (endometriosis and unopposed estrogen) associated with infertility, the low incidence of most of these cancers, and that the diagnosis of cancer is typically several years after fertility drug use. On the basis of available data, there does not appear to be an association between fertility drugs and breast, colon, or cervical cancer. There is no conclusive evidence that fertility drugs increase the risk of uterine cancer, although women with infertility are at higher risk of uterine cancer. There are insufficient data to comment on the risk of melanoma and non-Hodgkin lymphoma associated with fertility drug use. Women should be informed that there may be an increased risk of invasive and borderline ovarian cancers and thyroid cancer associated with fertility treatment. It is difficult to determine whether this risk is related to underlying endometriosis, female infertility, or nulliparity.

Keywords: Fertility; cancer; fertility drugs; reproductive health; reproductive science.

Καρκίνος ενδομητρίου

- Ο πιο συχνός γυναικολογικός καρκίνος στον αναπτυγμένο κόσμο και ο δεύτερος στον αναπτυσσόμενο κόσμο μετά τον καρκίνο του τραχήλου.
- Συνήθως, σε γυναίκες ηλικίας 50-65 ετών.
- 5% σε γυναίκες <40 ετών.
- 8-14% σε γυναίκες αναπαραγωγικής ηλικίας.
- Παράγοντες κινδύνου: PCOS, καθυστερημένη εμμηνόπαυση, πρώιμη εμμηναρχή, ατοκία, καθυστέρηση τεκνοποίησης, παχυσαρκία, ΣΔ, χρήση ταμοξιφαίνης, χορήγηση εξωγενών οιστογόνων, ορμονική ανισορροπία.
- Προστατευτικοί παράγοντες: Κύηση, ΑΟΔ.





Φάρμακα γονιμότητας και καρκίνος ενδομητρίου

Αναστασία Μπόθου, Επίκουρη Καθηγήτρια Μαιευτικής

American Journal of
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ORIGINAL CONTRIBUTIONS

Uterine Cancer after Use of Clomiphene Citrate to Induce Ovulation

Michelle D. Althuis[1], Kamran S. Moghissi[2], Carolyn L. Westhoff[3], Bert Scoccia[4], Emmet J. Lamb[5], Jay H. Lubin[1], and Louise A. Brinton[1]

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 ≥6 cycles), and time elapsed since initial use (RR = 2.50, 95% CI: 0.9, 7.2 for women followed for ≥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.

J Cancer Res Clin Oncol (2016) 142:287–293
DOI 10.1007/s00432-015-2035-x

ORIGINAL ARTICLE - CLINICAL ONCOLOGY

The risk of female malignancies after fertility treatments: a cohort study with 25-year follow-up

R. Kessous[1] · E. Davidson[3] · M. Meirovitz[1] · R. Sergienko[2] · E. Sheiner[1]

Abstract

Objective: To investigate whether an association exists between a history of fertility treatments and future risk of female malignancies.

Study design: A population-based study compared the incidence of long-term female malignancies in a cohort of women with and without a history of fertility treatments including in vitro fertilization (IVF) and ovulation induction (OI). Deliveries occurred between the years 1988-2013, with a mean follow-up duration of 12 years. Excluded from the study were women with known genetic predisposition for malignancies or known malignancies prior to the index pregnancy. Female malignancies were divided into specific types including ovarian, uterine, breast and cervix. Kaplan-Meier survival curve was used to estimate cumulative incidence of malignancies. Cox proportional hazard models were used to estimate the adjusted hazard ratios (HRs) for female malignancy.

Results: During the study period, 106,031 women met the inclusion criteria; 4.1 % (n = 4363) occurred in patients following fertility treatments. During the follow-up period, patients with a history of IVF treatments had a significantly increased risk of being diagnosed with ovarian and uterine cancer as compared to patients after OI and patients with no history of fertility treatments. Cox proportional hazard models were constructed for ovarian and uterine cancer separately, controlling for confounders such as maternal age and obesity. A history of IVF treatment remained independently associated with ovarian and uterine cancer (adjusted HR 3.9; 95 % CI 1.2-12.6; P = 0.022 and adjusted HR 4.6; 95 % CI 1.4-14.9; P = 0.011; respectively).

Conclusion: IVF treatments pose a significant risk of subsequent long-term ovarian and uterine cancer.

Human Reproduction, Vol.34, No.5 pp. 894–902, 2019
Advanced Access publication on March 13, 2019 doi:10.1093/humrep/dez018

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of cancer in infertile women: analysis of US claims data

Gayathree Murugappan[1,*], Shufeng Li[2], Ruth B. Lathi[1], Valerie L. Baker[3], and Michael L. Eisenberg[1,2]

STUDY QUESTION: Is female infertility associated with higher risk of cancer?

SUMMARY ANSWER: Although absolute risks are low, infertility is associated with higher risk of cancer compared to a group of non-infertile women.

WHAT IS KNOWN ALREADY: Infertile women are at higher risk of hormone-sensitive cancers. Information on risk of non-gynecologic cancers is rare and conflicting, and the effect of pregnancy on these risk associations is known for only a minority of cancer types.

STUDY DESIGN, SIZE, DURATION: Retrospective cohort analysis between 2003 and 2016 using an insurance claims database.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In all, 64 345 infertile women identified by infertility diagnosis, testing or treatment were compared to 3 128 345 non-infertile patients seeking routine gynecologic care. Women with prior diagnosis of cancer or within 6 months of index event were excluded. Main outcomes were development of any malignancy and individual cancers as identified by ICD-9/ICD-10 codes. Results were adjusted for age at index date, index year, nulliparity, race, smoking, obesity, number of visits per year and highest level of education.

MAIN RESULTS AND THE ROLE OF CHANCE: Infertile women had an overall higher risk of developing cancer compared to non-infertile women (2.0 versus 1.7%, adjusted hazard ratio (aHR) = 1.18; CI: 1.12–1.24). In addition, the risk of uterine cancer (0.10 versus 0.06%, aHR = 1.78; CI: 1.39–2.28), ovarian cancer (0.14 versus 0.09%, aHR 1.64; CI: 1.33–2.01), lung cancer (0.21 versus 0.21%, aHR = 1.38; CI: 1.01–1.88), thyroid cancer (0.21 versus 0.16%, aHR = 1.29; CI: 1.09–1.53), leukemia (0.10 versus 0.06%, aHR = 1.55; CI: 1.21–1.98) and liver and gallbladder cancer (0.05 versus 0.03%, aHR = 1.59; CI: 1.11–2.30) were higher in infertile women compared to non-infertile women. In a subgroup analysis of women in each cohort who became pregnant and had a delivery during enrollment, the risk of uterine and ovarian cancer were similar between infertile and non-infertile women. In a subgroup analysis excluding women with PCOS and endometriosis from both cohorts, the risk of uterine cancer was similar between infertile and non-infertile women.

LIMITATIONS, REASONS FOR CAUTION: Absolute risk of cancer was low, average follow up for each individual was limited, and average age at index date was limited. Insurance databases have known limitations.

WIDER IMPLICATIONS OF THE FINDINGS: Using claims-based data, we report that infertile women may have a higher risk of certain cancers in the years after infertility evaluation; continued follow up should be considered after reproductive goals are achieved.

Cancer in women after assisted reproductive technology

Barbara Luke, Sc.D., M.P.H.,[a] Morton B. Brown, Ph.D.,[b] Logan G. Spector, Ph.D.,[c] Stacey A. Missmer, Sc.D.,[d,e,f] Richard E. Leach, M.D.,[a] Melanie Williams, Ph.D.,[g] Lori Koch, B.A.,[h] Yolanda Smith, M.D., M.S.,[i] Judy E. Stern, Ph.D.,[j] G. David Ball, Ph.D.,[k] and Maria J. Schymura, Ph.D.[l]

Objective: To evaluate the risk of cancer after assisted reproductive technology (ART) therapy.
Design: Longitudinal cohort study.
Setting: Not applicable.
Patient(s): New York, Texas, and Illinois residents between 2004 and 2009, treated with ART, comprising cycles of 113,226 women, including 53,859 women without prior ART treatment, who were linked to their respective state cancer registries and whose cycles were reported to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS).
Intervention(s): None.
Main Outcome Measure(s): Diagnosis of cancer, as reported to the state cancer registry; standardized incidence ratios (SIR) and their 95% confidence intervals, comparing the observed to expected cancer cases based on age-specific cancer rates in the general population of each state.
Result(s): Among the cohort of women without prior ART therapy, hazard ratios (HR) and 95% confidence intervals (CI) were calculated for treatment parameters and reproductive history factors. The mean follow-up period was 4.87 years; among women without prior ART, 450 women developed 460 cancers. Women treated with ART had a statistically significantly lower risk for all cancers (for all women: SIR 0.78; CI, 0.73–0.83; women without prior ART: SIR 0.75; CI, 0.68–0.82), breast cancer, and all female genital cancers; a non-statistically-significant lower risk for endocrine and uterine cancer; and a non-statistically-significant higher risk for melanoma and ovarian cancer. Among women without prior ART, we found no statistically significant increased HR by parity, number of cycles, cumulative follicle-stimulating hormone dosage, or cycle outcome.
Conclusion(s): Women initiating ART treatment have no greater risk for developing cancer after nearly 5 years of follow-up compared with the general population and with other women treated with ART. (Fertil Steril® 2015;104:1218–26. ©2015 by American Society for Reproductive Medicine.)

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[Intervention Review]

Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility

Alkistis Skalkidou[1], Theodoros N Sergentanis[2], Spyros P Gialamas[2], Marios K Georgakis[2], Theodora Psaltopoulou[2], Marialena Trivella[3], Charalampos S Siristatidis[4], Evangelos Evangelou[5], Eleni Petridou[2]

Main results

Nineteen studies were eligible for inclusion (1,937,880 participants). Overall, the quality of evidence was very low, due to serious risk of bias and indirectness (non-randomised studies (NRS), which was reflected on the GRADE assessment.

Six eligible studies, including subfertile women, without a general population control group, found that exposure to any ovary-stimulating drug was not associated with an increased risk of endometrial cancer (RR 0.96, 95% CI 0.67 to 1.37; 156,774 participants; very low quality evidence). Fifteen eligible studies, using a general population as the control group, found an increased risk after exposure to any ovary-stimulating drug (RR 1.75, 95% CI 1.18 to 2.61; 1,762,829 participants; very low quality evidence).

Five eligible studies, confined to subfertile women (92,849 participants), reported on exposure to clomiphene citrate; the pooled studies indicated a positive association (RR 1.32; 95% CI 1.01 to 1.71; 88,618 participants; very low quality evidence), although only at high dosage (RR 1.69, 95% CI 1.07 to 2.68; two studies; 12,073 participants) and at a high number of cycles (RR 1.69, 95% CI 1.16 to 2.47; three studies; 13,757 participants). Four studies found an increased risk of endometrial cancer in subfertile women who required clomiphene citrate compared to a general population control group (RR 1.87, 95% CI 1.00 to 3.48; four studies, 19,614 participants; very low quality evidence). These data do not tell us whether the association is due to the underlying conditions requiring clomiphene or the treatment itself.

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[Intervention Review]

Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility

Alkistis Skalkidou[1], Theodoros N Sergentanis[2], Spyros P Gialamas[2], Marios K Georgakis[2], Theodora Psaltopoulou[2], Marialena Trivella[3], Charalampos S Siristatidis[4], Evangelos Evangelou[5], Eleni Petridou[2]

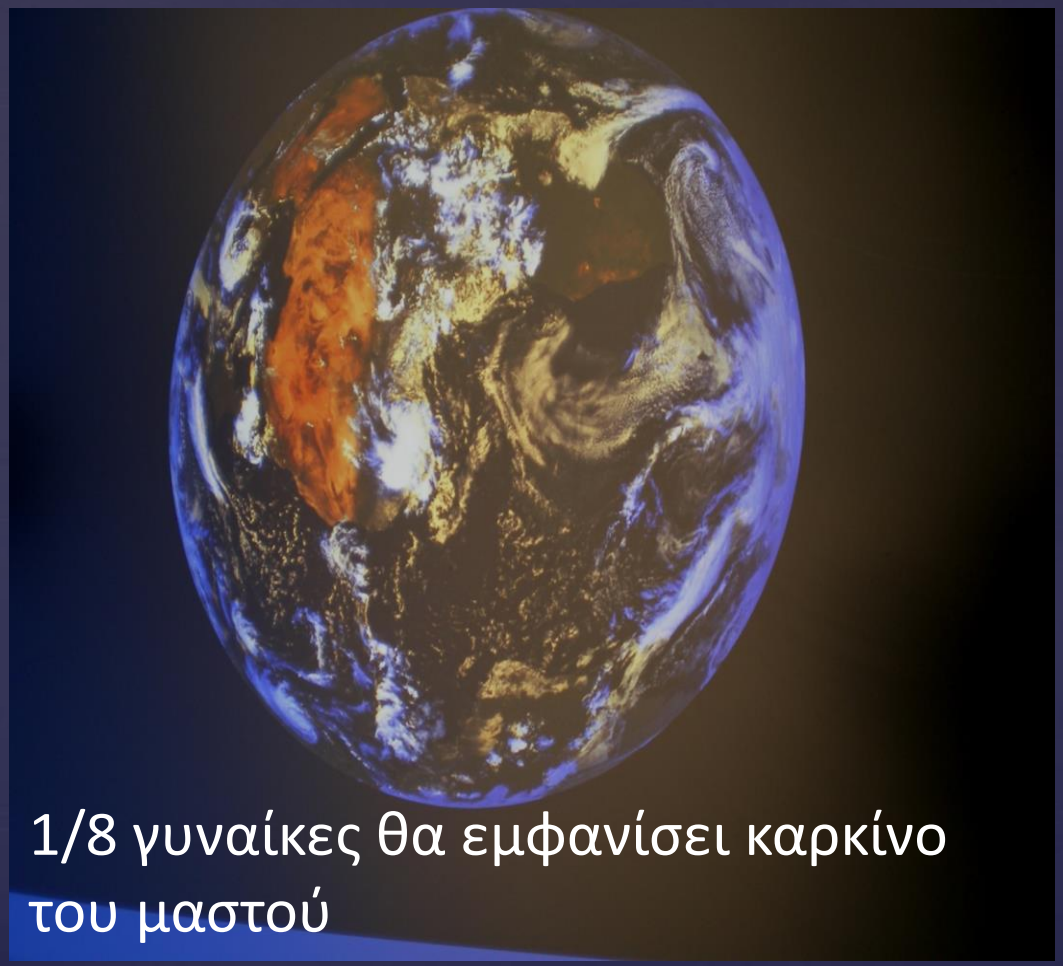
Using unexposed subfertile women as controls, exposure to gonadotropins was associated with an increased risk of endometrial cancer (RR 1.55, 95% CI 1.03 to 2.34; four studies; 17,769 participants; very low quality evidence). The respective analysis of two studies (1595 participants) versus the general population found no difference in risk (RR 2.12, 95% CI 0.79 to 5.64: very low quality evidence).

Exposure to a combination of clomiphene citrate and gonadotropins, compared to unexposed subfertile women, produced no difference in risk of endometrial cancer (RR 1.18, 95% CI 0.57 to 2.44; two studies; 6345 participants; very low quality evidence). However, when compared to the general population, an increased risk was found , suggesting that the key factor might be subfertility, rather than treatment (RR 2.99, 95% CI 1.53 to 5.86; three studies; 7789 participants; very low quality evidence).

Authors' conclusions

The synthesis of the currently available evidence does not allow us to draw robust conclusions, due to the very low quality of evidence. It seems that exposure to clomiphene citrate as an ovary-stimulating drug in subfertile women is associated with increased risk of endometrial cancer, especially at doses greater than 2000 mg and high (more than 7) number of cycles. This may largely be due to underlying risk factors in women who need treatment with clomiphene citrate, such as polycystic ovary syndrome, rather than exposure to the drug itself. The evidence regarding exposure to gonadotropins was inconclusive.

Καρκίνος μαστού



1/8 γυναίκες θα εμφανίσει καρκίνο του μαστού

Αναστασία Μπόθου, Επίκουρη Καθηγήτρια Μαιευτικής

Επιδημιολογία καρκίνου του μαστού: Συχνότητα – Θνησιμότητα

Παγκόσμια:

- **>2*10^6 νέες περιπτώσεις/ανά έτος.**
- **2η αιτία θνησιμότητας από καρκίνο στις γυναίκες μετά από τον καρκίνο του πνεύμονα (≈15%).**

(Ιατράκης 2018, Taghian et al 2019)

- **Ο κίνδυνος ανάπτυξης καρκίνου του μαστού σε κάθε γυναίκα στις ΗΠΑ είναι 1 στις 8 γυναίκες, ενώ στην Ευρώπη είναι 1 στις 10 στη διάρκεια της ζωής τους.**

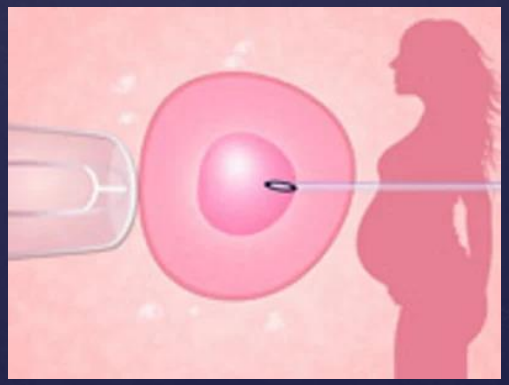
(Desantis et al 2017)

Δυστυχώς, στην Ελλάδα δεν υπάρχει εθνικό σύστημα καταγραφής των περιπτώσεων καρκίνου του μαστού, οπότε τα στοιχεία που διαθέτουμε βασίζονται στη διεθνή βιβλιογραφία.

Φάρμακα γονιμότητας και καρκίνος του μαστού

- Η κοινή πεποίθηση είναι, ότι οι θεραπείες γονιμότητας μπορεί να προκαλέσουν προσωρινά υψηλά επίπεδα οιστρογόνων και προγεστερόνης στο αίμα και, ως εκ τούτου, έχει προταθεί, ότι συνδέονται με αύξηση της συχνότητας εμφάνισης καρκίνου του μαστού, ιδίως σε επαναλαμβανόμενη και παρατεταμένη χρήση.
- Η ατοκία, η προχωρημένη ηλικία κατά τον πρώτο τοκετό, η καθυστερημένη εμμηνόπαυση και η υπογονιμότητα θεωρούνται παράγοντες κινδύνου για την εμφάνιση καρκίνου του μαστού και, ταυτόχρονα, χαρακτηριστικά του πληθυσμού με υπογονιμότητα.
- Η πλειονότητα των μελετών και όλες οι ανασκοπήσεις και οι μετααναλύσεις δεν έδειξαν σημαντική αύξηση στον κίνδυνο εμφάνισης καρκίνου του μαστού, ούτε μείωση του κινδύνου μετά από θεραπεία υπογονιμότητας, είτε σε σύγκριση με υπογόνιμες γυναίκες, οι οποίες δεν υποβλήθηκαν σε θεραπεία με φάρμακα γονιμότητας, είτε σε σύγκριση με τον γενικό πληθυσμό.

Kessous et al 2016. The risk of female malignancies after fertility treatments: a cohort study with 25-year follow-up. J Cancer Res Clin Oncol, 142 (2016), pp. 287-293



Breast Cancer Res Treat (2015) 150:405–413
DOI 10.1007/s10549-015-3328-0

EPIDEMIOLOGY

Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies

Alessandra Gennari · Mauro Costa · Matteo Puntoni · Laura Paleari · Andrea De Censi · Maria Pia Sormani · Nicoletta Provinciali · Paolo Bruzzi

Abstract The increasing practice of hormonal infertility treatments (HITs) raised concerns about their effects on breast cancer (BC) risk. Available evidence reported conflicting results. The aim of this study was to assess the potential association between HITs and BC risk. The literature was searched through November 2014. Eligible studies included cohort studies reporting BC incidence in women undergone HITs. Data were analyzed with standard meta-analytic techniques. Subgroup analyses were performed by type of intervention (IVF vs. NO IVF), follow-up duration (<10 vs. >10 years), and type of control (population vs. infertile). 20 eligible studies (207.914 women, 2347 BC) were retrieved: no increased risk was detected (SRR = 1.05, 95 % CI 0.96–1.14), with a significant heterogeneity ($I^2 = 59$ %, $p = 0.001$) among studies. In the seven studies with the in vitro fertilization (IVF) procedure, no increase in BC risk was observed (SRR = 0.96, 95 % CI 0.80–1.14); in the three NO IVF studies, an increased BC risk was identified (SRR = 1.26, 95 %CI 1.06–1.50). A borderline interaction between type of intervention (IVF vs. NO IVF) and BC risk was observed ($p = 0.06$). An increased risk with longer follow-up (≥10 vs. <10 years) was detected (SRR = 1.13, 95 % CI 1.02–1.26 vs. SRR = 0.95, 95 % CI 0.85–1.06). Overall, HITs are not associated with an increased BC risk. In particular, no increased risk was observed in women undergoing IVF. Conversely, an increased in BC risk cannot be ruled out with older treatment protocols based on clomiphene. The long-term administration of clomiphene outside the current indications should be discouraged because of a possible increase in BC risk.

Keywords Hormonal infertility treatments · Breast cancer risk · Cohort studies

In vitro fertilization and breast cancer: is there cause for concern?

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Objective: To examine the incidence rate of breast cancer in a cohort of women undergoing treatment for infertility, comparing the rate in women who had in vitro fertilization (IVF) with those who did not.
Design: Population-based cohort study using linked hospital and registry data.
Setting: Hospital.
Patient(s): All women aged 20–44 years seeking hospital investigation and treatment for infertility in Western Australia during the period 1983–2002 (n = 21,025).
Intervention(s): None.
Main Outcome Measure(s): Hazard ratios (HRs) for breast cancer.
Result(s): There was no overall increase in the rate of breast cancer in women who had IVF (HR 1.10, 95% confidence interval [CI] 0.88–1.36), but there was an increased rate in women who commenced IVF at a young age. Women who commenced hospital infertility treatment at 24 years and required IVF had an unadjusted HR of breast cancer of 1.59 (95% CI 1.05–2.42) compared with women of the same age who had infertility treatment but no IVF. When adjusted for late age at first delivery, which is associated with an increased rate of breast cancer, and delivery of twins and higher-order multiples, which is associated with a decreased rate of breast cancer, the HR remained elevated at 1.56 (95% CI 1.01–2.40). Hazard ratios were not elevated in women who commenced treatment at age 40 and required IVF (adjusted HR 0.87, 95% CI 0.62–1.22).
Conclusion(s): Commencing IVF treatment at a young age is associated with an increased rate of breast cancer. (Fertil Steril® 2012;98:334–40. ©2012 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, breast cancer, Cox regression, hazard ratios

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ELSEVIER

Fertility and Sterility
Volume 98, Issue 2, August 2012, Pages 334-340

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Long-term Relationship of Ovulation-Stimulating Drugs to Breast Cancer Risk

Louise A. Brinton[1], Bert Scoccia[4], Kamran S. Moghissi[5], Carolyn L. Westhoff[6], Shelley Niwa[2], David Ruggieri[3], Britton Trabert[1], and Emmet J. Lamb[7]

Abstract

Background: Although fertility drugs stimulate ovulation and raise estradiol levels, their effect on breast cancer risk remains unresolved.

Methods: An extended follow-up was conducted among a cohort of 12,193 women evaluated for infertility between 1965 and 1988 at five U.S. sites. Follow-up through 2010 was achieved for 9,892 women (81.1% of the eligible population) via passive as well as active (questionnaires) means. Cox regression determined HRs and 95% confidence intervals (CI) for fertility treatments adjusted for breast cancer risk factors and causes of infertility.

Results: During 30.0 median years of follow-up (285,332 person-years), 749 breast cancers were observed. Ever use of clomiphene citrate among 38.1% of patients was not associated with risk (HR = 1.05; 95% CI, 0.90–1.22 vs. never use). However, somewhat higher risks were seen for patients who received multiple cycles, with the risk for invasive cancers confirmed by medical records being significantly elevated (HR = 1.69; 95% CI, 1.17–2.46). This risk remained relatively unchanged after adjustment for causes of infertility and multiple breast cancer predictors. Gonadotropins, used by 9.6% of patients, mainly in conjunction with clomiphene, showed inconsistent associations with risk, although a significant relationship of use with invasive cancers was seen among women who remained nulligravid (HR = 1.98; 95% CI, 1.04–3.60).

Conclusions: Although the increased breast cancer risk among nulligravid women associated with gonadotropins most likely reflects an effect of underlying causes of infertility, reasons for the elevated risk associated with multiple clomiphene cycles are less clear.

Impact: Given our focus on a relatively young population, additional evaluation of long-term fertility drug effects on breast cancer is warranted. *Cancer Epidemiol Biomarkers Prev; 23(4); 584–93. ©2014 AACR.*

Gynecol Endocrinol. 2012 Oct;28(10):809-14. doi: 10.3109/09513590.2012.671391. Epub 2012 Apr 5.

Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up

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Affiliations + expand

PMID: 22475084 DOI: 10.3109/09513590.2012.671391

Abstract

The aim of the present study was to evaluate the possible risk for cancer development in infertile women with over 30 years of follow-up. Cancer development was assessed through linkage with the National Cancer Registry updated to 31 December 2005 in a cohort of 2431 women who were treated for infertility at the Sheba Medical Center in Israel during the period 1964-1974 and contributed more than 84,000 women years of follow-up. Standardized incidence ratios (SIR) were calculated between the observed cancer cases and the expected cancer rates in the general population. The mean age at the end of follow-up was 62.7 years. Eighteen cases of ovarian cancer were observed as compared to 18.1 expected (SIR = 1.0; 95% CI = 0.59-1.57). For breast cancer, 153 cases were observed as compared to 131.9 expected (SIR = 1.16; 95% CI = 0.98-1.36), and for endometrial cancer, 30 cases were observed as compared to 17.8 expected cases (SIR = 1.69; 95% CI = 1.14-2.41). No excess risk associated with exposure to gonadotropins was observed. Infertility was found to be associated with significant increased risk for endometrial cancer and borderline increased risk for breast cancer. Ovarian cancer risk was not found to be elevated. No significant excess risk was associated with treatment with ovulation induction.

JAMA. 2016 Jul 19;316(3):300-12. doi: 10.1001/jama.2016.9389.

Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer

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Abstract

Importance: Previous studies of breast cancer risk after in vitro fertilization (IVF) treatment were inconclusive due to limited follow-up.

Objective: To assess long-term risk of breast cancer after ovarian stimulation for IVF.

Design, setting, and participants: Historical cohort (OMEGA study) with complete follow-up through December 2013 for 96% of the cohort. The cohort included 19,158 women who started IVF treatment between 1983 and 1995 (IVF group) and 5950 women starting other fertility treatments between 1980 and 1995 (non-IVF group) from all 12 IVF clinics in the Netherlands. The median age at end of follow-up was 53.8 years for the IVF group and 55.3 years for the non-IVF group.

Conclusions and relevance: Among women undergoing fertility treatment in the Netherlands between 1980 and 1995, IVF treatment compared with non-IVF treatment was not associated with increased risk of breast cancer after a median follow-up of 21 years. Breast cancer risk among IVF-treated women was also not significantly different from that in the general population. These findings are consistent with absence of a significant increase in long-term risk of breast cancer among IVF-treated women.

Original Study

Breast Cancer and Ovulation Induction Treatments

Robabeh Taheripanah,[1] Firoozeh Balash,[1] Robab Anbiaee,[2]
Mohammedreza Mahmoodi,[3] Azadeh Akbari Sene[4]

Abstract

In this case control study of 928 women with breast cancer and 928 controls, we found no statistically significant relationship between infertility and ovulation induction drugs with the risk of breast cancer development, except for significant increases in the risk of breast cancer among patients who had used human menopausal gonadotropin for >6 months.

Background: This study was performed to determine whether the use of ovulation induction drugs in treatment of infertility have a significant effect on the risk of breast cancer. **Patients and Methods:** This case control study (928 cases, 928 controls), was performed in the gynecology and oncology clinics of Shahid Beheshti University of Medical Sciences between 2011 and 2013. Data were collected via in-person interviews using a questionnaire, which included demographic and gynecologic information. Statistical analysis was performed using SPSS statistics software version 20 (IBM Corp). **Results:** The use of ovulation induction drugs was not significantly associated with an increased risk of breast cancer (odds ratio [OR], 1.13; 95% confidence interval [CI], 0.7-1.855) among women with infertility (OR, 1.28; 95% CI, 0.8-1.95). **Conclusion:** We observed no statistically significant relationship between infertility and ovulation induction drugs with the risk of breast cancer, except for significant increases in the risk of breast cancer among patients who had used fertility drugs for >6 months.

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Keywords: Breast cancer, Clomiphene, Gonadotropins, Infertility, Ovarian stimulation

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DOI: 10.26355/eurrev_201811_16434

Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors

L. Del Pup, F. A. Peccatori, P.E. Levi-Setti, G. Codacci-Pisanelli, P. Patrizio

OBJECTIVE: Infertile women requiring ovarian stimulation and assisted reproduction techniques (ART) are faced with difficult issues. The fear that using hormones could increase their risk of cancer is the most significant. One of the main challenges for assessing cancer risk after ART is the difficulty to separate it from the underlying condition of infertility per se. The delay or the inability to achieve a pregnancy is an important risk factor for breast, endometrial and ovarian cancer. We analyzed the current literature on the topic.

MATERIALS AND METHODS: The published literature in Medline and Cochrane was screened using the following keywords: ovulation induction, reproductive techniques, clomiphene, in vitro fertilization, fertility agents, female/adverse effects, female/toxicity gonadotropins/ adverse effects or gonadotropins/toxicity and "neoplasms or cancer".

RESULTS: A total of 95 articles were evaluated. Limited evidence suggests that high doses or many cycles of clomiphene citrate could increase the risk of endometrial cancer, although the confounding factors of polycystic ovarian disease and overweight are not always considered. In some studies, ART modestly increased the risk of borderline ovarian cancer. Fertility treatments do not increase the risk of breast, cervical, endometrial and ovarian cancers, thyroid, melanoma and colon cancer.

CONCLUSIONS: Women can be reassured that fertility drugs do not appear to significantly increase the risk of invasive ovarian, endometrial, breast or other cancers, while achieving a pregnancy at an earlier age is a significant protective factor.

Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome

Oranite Goldrat [a,b], Niels Kroman [c], Fedro A. Peccatori [d], Octavi Cordoba [e], Barbara Pistilli [f], Oejvind Lidegaard [g], Isabelle Demeestere [b], Hatem A. Azim Jr. [h,*]

Abstract ***Introduction and aims:*** We have previously shown that pregnancy is safe following breast cancer, even in endocrine sensitive disease. Yet infertility remains common following systemic treatment. To date, no study has evaluated the safety of assisted reproductive technology (ART) after breast cancer treatment. In this study, we evaluated the impact of ART on pregnancy and long-term outcomes of young breast cancer survivors.

Methods: This is a multi-centre retrospective study in which women who were diagnosed with breast cancer between 2000 and 2009, and had a pregnancy following breast cancer diagnosis were eligible. Patients were divided into two groups according to whether ART following primary systemic therapy was performed to achieve pregnancy. We evaluated the association between ART use and clinic-pathological characteristics, pregnancy outcome and long-term breast cancer outcome.

Results: A total of 198 patients were evaluated; of whom 25 underwent ART. No significant differences in tumour characteristics were observed between both groups, except for histological grade 3 tumours, which were fewer in the ART group (36% versus 59%, $p = 0.033$). Around 90% of patients received primary adjuvant chemotherapy and more than 50% had an endocrine sensitive disease. Patients in the ART group were older at diagnosis (31.4 versus 33.7 years, $p = 0.009$), at conception (38 versus 35 years, $p < 0.001$), and experienced more miscarriages (23.5 versus 12.6%, $p = 0.082$). Full term pregnancies were achieved in 77% and 76% of the spontaneous and ART groups, respectively. Mean follow-up between conception and last follow-up was 63 and 50 months in the spontaneous and ART groups, respectively with no difference in breast cancer outcome observed between the two groups ($p = 0.54$).

Conclusion: Pregnancy using ART in women with history of breast cancer is feasible and does not seem to be detrimental to cancer outcome. Larger studies are needed to further confirm this observation.

ORIGINAL ARTICLES: ASSISTED REPRODUCTION

Check for updates

Influence of subfertility and assisted reproductive technology treatment on mortality of women after delivery

Charles C. Coddington, M.D.,[a,b] Daksha Gopal, M.P.H.,[c] Xiaohui Cui, Ph.D.,[d] Howard Cabral, Ph.D.,[c] Hafsatou Diop, M.D.,[d] and Judy E. Stern, Ph.D.[e]

Objective: To compare incidence, risk factors, and etiology of women's deaths in fertile, subfertile, and undergoing assisted reproductive technology (ART) in the years after delivery.
Design: Retrospective cohort.
Setting: University hospital.
Patient(s): Women who had delivered in Massachusetts.
Intervention(s): This study used data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System linked to vital records, hospital stays, and the Massachusetts death file. Mortality of patients delivered from 2004–2013 was evaluated through 2015. The exposure groups, determined on the basis of the last delivery, were ART-treated (linked to Society for Assisted Reproductive Technology Clinic Outcome Reporting System), subfertile (no ART but with indicators of subfertility including birth certificate checkbox for fertility treatment, prior hospitalization for infertility [International Classification of Disease codes 9 628 or V23], and/or prior delivery with checkbox or ART), or fertile (neither ART nor subfertile). Numbers (per 100,000 women-years) and causes of death were obtained from the Massachusetts death file.
Main Outcome Measure(s): Mortality of women after delivery in each of the three fertility groups and the most common etiology of death in each.
Result(s): We included 483,547 women: 16,429 ART, 11,696 subfertile, and 455,422 fertile among whom there were 1,280 deaths with 21.1, 25.5, and 44.7 deaths, respectively, per 100,000 women-years. External causes (violence, accidents, and poisonings) were the most common reasons for death in the fertile group. Deaths occurred on average 46 months after delivery. When external causes of death were removed, there were 19.1, 17.0, and 25.6 deaths per 100,000 women-years and leading causes of death in all groups were cancer and circulatory problems.
Conclusion(s): The study presents reassuring data that death rates within 5 years of delivery in ART-treated and subfertile women do not differ from those in fertile women. (Fertil Steril® 2020;113:569-77. ©2019 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Comparative Study > Int J Cancer. 2015 Mar 1;136(5):1140-8. doi: 10.1002/ijc.29069. Epub 2014 Jul 16.

Risk of breast cancer following fertility treatment--a registry based cohort study of parous women in Norway

Marte Myhre Reigstad [1], Inger Kristin Larsen, Tor Åge Myklebust, Trude Eid Robsahm, Nan Birgitte Oldereid, Anne Katerine Omland, Siri Vangen, Louise Annette Brinton, Ritsa Storeng

Abstract

Despite increasing numbers of women availing themselves of assisted reproductive technology (ART), effects on cancer risk remain unresolved. Given hormonal exposures, breast cancer risk is of particular concern. The aim of this study is to investigate breast cancer risk amongst women giving birth following ART as compared to that amongst women who gave birth without ART. Data on all women who gave birth in Norway with or without ART, between 1984 and 2010 were obtained from the Medical Birth Registry of Norway (MBRN). 808,834 women eligible for study were linked to the Cancer Registry of Norway. Cox proportional models computed hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer between the two groups, adjusting for age, parity, age at first birth, calendar period and region of residence. In total, 8,037 women were diagnosed with breast cancer during the study period, 138 ART women and 7,899 unexposed. Total follow-up time was 12,401,121 person-years (median 16.0); median age at entry was 32.5 years (range 18.6-49.9) for ART women and 26.3 (range 10.5-54.6) for unexposed. Women exposed to ART had an elevated risk of breast cancer (adjusted HR 1.20, 95% CI 1.01-1.42). Subgroup analyses gave an HR of 1.30 (95% CI 1.07-1.57) for women treated with IVF and 1.35 (95 % CI 1.07-1.71) for women with follow-up >10 years, compared with controls. Our findings of increased risk in the study population warrant continued monitoring of women treated with ART as this population advances into more typical cancer age ranges.

Human Reproduction, Vol.34, No.5 pp. 894–902, 2019
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human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of cancer in infertile women: analysis of US claims data

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STUDY DESIGN, SIZE, DURATION: Retrospective cohort analysis between 2003 and 2016 using an insurance claims database.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In all, 64 345 infertile women identified by infertility diagnosis, testing or treatment were compared to 3 128 345 non-infertile patients seeking routine gynecologic care. Women with prior diagnosis of cancer or within 6 months of index event were excluded. Main outcomes were development of any malignancy and individual cancers as identified by ICD-9/ICD-10 codes. Results were adjusted for age at index date, index year, nulliparity, race, smoking, obesity, number of visits per year and highest level of education.

MAIN RESULTS AND THE ROLE OF CHANCE: Infertile women had an overall higher risk of developing cancer compared to non-infertile women (2.0 versus 1.7%, adjusted hazard ratio (aHR) = 1.18; CI: 1.12–1.24). In addition, the risk of uterine cancer (0.10 versus 0.06%, aHR = 1.78; CI: 1.39–2.28), ovarian cancer (0.14 versus 0.09%, aHR 1.64; CI: 1.33–2.01), lung cancer (0.21 versus 0.21%, aHR = 1.38; CI: 1.01–1.88), thyroid cancer (0.21 versus 0.16%, aHR = 1.29; CI: 1.09–1.53), leukemia (0.10 versus 0.06%, aHR = 1.55; CI: 1.21–1.98) and liver and gallbladder cancer (0.05 versus 0.03%, aHR = 1.59; CI: 1.11–2.30) were higher in infertile women compared to non-infertile women. In a subgroup analysis of women in each cohort who became pregnant and had a delivery during enrollment, the risk of uterine and ovarian cancer were similar between infertile and non-infertile women. In a subgroup analysis excluding women with PCOS and endometriosis from both cohorts, the risk of uterine cancer was similar between infertile and non-infertile women.

OPEN ACCESS

Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation

Carrie L Williams,[1] Michael E Jones,[2] Anthony J Swerdlow,[2] Beverley J Botting,[1] Melanie C Davies,[3] Ian Jacobs,[3,4] Kathryn J Bunch,[5] Michael F G Murphy,[6] Alastair G Sutcliffe[1]

Results: 255 786 women contributed 2 257 789 person years' follow-up. No significant increased risk of corpus uteri cancer (164 cancers observed *v* 146.9 cancers expected; SIR 1.12, 95% confidence interval 0.95 to 1.30) was found during an average of 8.8 years' follow-up. This study found no significantly increased risks of breast cancer overall (2578 *v* 2641.2; SIR 0.98, 0.94 to 1.01) or invasive breast cancer (2272 *v* 2371.4; SIR 0.96, 0.92 to 1.00). An increased risk of in situ breast cancer (291 *v* 253.5; SIR 1.15, 1.02 to 1.29; absolute excess risk (AER) 1.7 cases per 100 000 person years, 95% confidence interval 0.2 to 3.2) was detected, associated with an increasing number of treatment cycles (P=0.03). There was an increased risk of ovarian cancer (405 *v* 291.82; SIR 1.39, 1.26 to 1.53; AER 5.0 cases per 100 000 person years, 3.3 to 6.9), both invasive (264 *v* 188.1; SIR 1.40, 1.24 to 1.58; AER 3.4 cases per 100 000 person years, 2.0 to 4.9) and borderline (141 *v* 103.7; SIR 1.36, 1.15 to 1.60; AER 1.7 cases per 100 000 person years, 0.7 to 2.8). Increased risks of ovarian tumours were limited to women with endometriosis, low parity, or both. This study found no increased risk of any ovarian tumour in women treated because of only male factor or unexplained infertility.

Conclusions: No increased risk of corpus uteri or invasive breast cancer was detected in women who had had assisted reproduction, but increased risks of in situ breast cancer and invasive and borderline ovarian tumours were found in this study. Our results suggest that ovarian tumour risks could be due to patient characteristics, rather than assisted reproduction itself, although both surveillance bias and the effect of treatment are also possibilities. Ongoing monitoring of this population is essential.

BMJ. 2018 Jul 11:362:k2644. doi: 10.1136/bmj.k2644.

Gynecol Endocrinol. 2012 Oct;28(10):809-14. doi: 10.3109/09513590.2012.671391. Epub 2012 Apr 5.

Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up

Liat Lerner-Geva [1], Jaron Rabinovici, Liraz Olmer, Tzvia Blumstein, Shlomo Mashiach, Bruno Lunenfeld

Affiliations + expand

PMID: 22475084 DOI: 10.3109/09513590.2012.671391

Abstract

The aim of the present study was to evaluate the possible risk for cancer development in infertile women with over 30 years of follow-up. Cancer development was assessed through linkage with the National Cancer Registry updated to 31 December 2005 in a cohort of 2431 women who were treated for infertility at the Sheba Medical Center in Israel during the period 1964-1974 and contributed more than 84,000 women years of follow-up. Standardized incidence ratios (SIR) were calculated between the observed cancer cases and the expected cancer rates in the general population. The mean age at the end of follow-up was 62.7 years. Eighteen cases of ovarian cancer were observed as compared to 18.1 expected (SIR = 1.0; 95% CI = 0.59-1.57). For breast cancer, 153 cases were observed as compared to 131.9 expected (SIR = 1.16; 95% CI = 0.98-1.36), and for endometrial cancer, 30 cases were observed as compared to 17.8 expected cases (SIR = 1.69; 95% CI = 1.14-2.41). No excess risk associated with exposure to gonadotropins was observed. Infertility was found to be associated with significant increased risk for endometrial cancer and borderline increased risk for breast cancer. Ovarian cancer risk was not found to be elevated. No significant excess risk was associated with treatment with ovulation induction.

Breast J. 2008 Nov-Dec;14(6):517-22. doi: 10.1111/j.1524-4741.2008.00641.x. Epub 2008 Oct 14.

Beginning IVF treatments after age 30 increases the risk of breast cancer: results of a case-control study

Daniela Katz [1], Ora Paltiel, Tamar Peretz, Ariel Revel, Nir Sharon, Bella Maly, Nadav Michan, Miri Sklair-Levy, Tanir Allweis

Affiliations + expand

PMID: 19000041 DOI: 10.1111/j.1524-4741.2008.00641.x

Abstract

The long-term risks of in vitro fertilization (IVF) treatment remain unclear. This study was designed to determine breast cancer risk factors in women who underwent IVF, and to establish characteristics of these tumors. Records of 7,162 consecutive women who underwent IVF at a single center between 1984 and 2002 were linked with the Israel Cancer Registry to identify women who developed breast cancer. IVF-related parameters were compared between 28 breast cancer patients who had undergone IVF (IVF BC) and for whom complete IVF data were available with 140 women who underwent IVF and did not develop breast cancer (IVF non-BC). Tumor parameters were compared between 38 patients who developed breast cancer after IVF and 114 age-matched breast cancer patients who did not undergo IVF (non-IVF BC). Age over 30 at the time of first IVF treatment, even after controlling for age at first birth, was the only parameter significantly associated with increased breast cancer risk (RR = 1.24, p = 0.02, 95% CI = 1.03-1.48). There were no differences between IVF-BC and IVF non-BC patients in all other IVF-related parameters. The only statistically significant difference in tumors developing in IVF-BC patients compared with non-IVF BC patients was in grade distribution, particularly for grade II tumors. However, the significance of such a difference is unclear. Women who start IVF after the age of 30 appear to be at increased risk of developing breast cancer. The characteristics of breast tumors in women who underwent IVF are no different than in patients without previous exposure to IVF.

Breast Cancer Res Treat (2015) 150:405–413
DOI 10.1007/s10549-015-3328-0

EPIDEMIOLOGY

Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies

Alessandra Gennari · Mauro Costa · Matteo Puntoni · Laura Paleari · Andrea De Censi · Maria Pia Sormani · Nicoletta Provinciali · Paolo Bruzzi

Abstract The increasing practice of hormonal infertility treatments (HITs) raised concerns about their effects on breast cancer (BC) risk. Available evidence reported conflicting results. The aim of this study was to assess the potential association between HITs and BC risk. The literature was searched through November 2014. Eligible studies included cohort studies reporting BC incidence in women undergone HITs. Data were analyzed with standard meta-analytic techniques. Subgroup analyses were performed by type of intervention (IVF vs. NO IVF), follow-up duration (<10 vs. >10 years), and type of control (population vs. infertile). 20 eligible studies (207.914 women, 2347 BC) were retrieved: no increased risk was detected (SRR = 1.05, 95 % CI 0.96–1.14), with a significant heterogeneity ($I^2 = 59$ %, $p = 0.001$) among studies. In the seven studies with the in vitro fertilization (IVF) procedure, no increase in BC risk was observed (SRR = 0.96, 95 % CI 0.80–1.14); in the three NO IVF studies, an increased BC risk was identified (SRR = 1.26, 95 %CI 1.06–1.50). A borderline interaction between type of intervention (IVF vs. NO IVF) and BC risk was observed ($p = 0.06$). An increased risk with longer follow-up (>10 vs. <10 years) was detected (SRR = 1.13, 95 % CI 1.02–1.26 vs. SRR = 0.95, 95 % CI 0.85–1.06). Overall, HITs are not associated with an increased BC risk. In particular, no increased risk was observed in women undergoing IVF. Conversely, an increased in BC risk cannot be ruled out with older treatment protocols based on clomiphene. The long-term administration of clomiphene outside the current indications should be discouraged because of a possible increase in BC risk.

Keywords Hormonal infertility treatments · Breast cancer risk · Cohort studies

Reproductive BioMedicine Online (2010) 21, 266–271

www.sciencedirect.com
www.rbmonline.com

ARTICLE

Breast cancer diagnosis following ovarian stimulation: Are the tumours different?

Murat Sönmezer [a,b,*], Aylin Pelin Cil [c], Ozgur Oktem [d], Kutluk Oktay [e]

Abstract Demographic data and tumour characteristics of 18 patients (study group) diagnosed with breast cancer within 24 months of undergoing ovarian stimulation with either gonadotrophins or clomiphene citrate were evaluated and compared with similar 102 age-matched women diagnosed with breast cancer without prior infertility treatment (control group). Eight out of 17 (47.1%) patients in the study group and 35/95 (36.8%) patients in the control group had positive family history for breast cancer. Median tumour size was similar in the study and control groups (both 1.3 cm). Both groups were comparable regarding tumour histological types and oestrogen receptor, progesterone receptor and *Her2/Neu* expression status. Albeit not significant, stage 0 tumours were more prevalent in the study group compared with the control group (22.2% versus 10.5%), and there were no stage III tumours in the study group as opposed to 7/95 in the control group. In conclusion, breast cancer diagnosed within the first 2 years following infertility treatment is similar in tumour characteristics compared with those occurring in patients without prior infertility treatment.

KEYWORDS: breast cancer, family history, *Her2/Neu*, oestrogen receptor, ovulation induction, progesterone receptor

› Gynecol Endocrinol. 2012 Oct;28(10):809-14. doi: 10.3109/09513590.2012.671391. Epub 2012 Apr 5.

Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up

Liat Lerner-Geva [1], Jaron Rabinovici, Liraz Olmer, Tzvia Blumstein, Shlomo Mashiach, Bruno Lunenfeld

Affiliations + expand

PMID: 22475084 DOI: 10.3109/09513590.2012.671391

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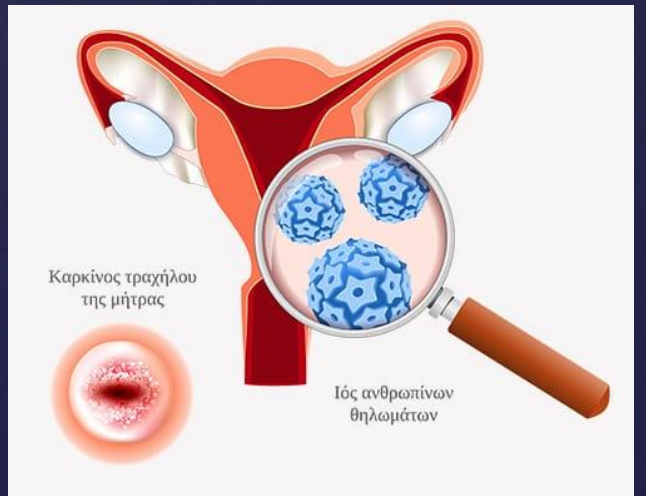
Καρκίνος τραχήλου μήτρας

- Ο καρκίνος του τραχήλου της μήτρας είναι ο πέμπτος πιο συχνός καρκίνος στις γυναίκες στην Ευρώπη και η τέταρτη πιο συχνή γυναικολογική κακοήθεια.
- 90% των περιπτώσεων οφείλεται στον HPV.
- Μέση ηλικία διάγνωσης τα 48 έτη (35-55).
- Κλινική εκδήλωση: Κολπική αιμορραγία μετά από σεξουαλική επαφή ή αυτόματα, αιματουρία, δύσοσμη κολπική υπερέκκριση, αιμορραγία από το ορθό, πόνος στην πλάτη ή τα κάτω άκρα, αναιμία.

- Πολλαπλές μελέτες έχουν αξιολογήσει τον κίνδυνο καρκίνου του τραχήλου της μήτρας μετά τη χρήση φαρμάκων γονιμότητας και δεν διαπίστωσαν αυξημένο κίνδυνο σε σύγκριση με αυτόν του γενικού πληθυσμού, καθώς και των ασθενών με υπογονιμότητα.

Li L, Zhou J, Qian XJ, Chen YD. Meta-analysis on the possible association between in vitro fertilization and cancer risk. Int J Gynecol Cancer, 23 (2013), pp. 16-24.
Siristatidis C, Sergentanis TN, Kanavidis P, Trivella M, Sotiraki M, Mavromatis I, et al. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis.Hum Reprod Update, 19 (2013), pp. 105-123.



Human Reproduction Vol.22, No.2 pp. 421–426, 2007 doi:10.1093/humrep/del411
Advance Access publication October 27, 2006.

Tumour incidence in Swedish women who gave birth following IVF treatment

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BACKGROUND: Possible effects on maternal tumour incidence of a full-term pregnancy following IVF treatment with indicated supraphysiologic steroid and peptide hormonal levels in pregnancy remain uncertain. METHODS: National registries were used to compare incidence of non-invasive and invasive tumour disease in Swedish women with live birth following IVF treatment with women with live birth without IVF. RESULTS: The study had a mean follow-up period of 6.2 years in the IVF group and 7.8 years in the non-IVF group, and the mean gestation period (s.d.) for IVF and non-IVF group was 271.0 (21.1) days and 278.5 (14.1) days, respectively. In a multivariate Poisson regression analysis, adjusted rate ratios of 0.70 (0.52–0.92) and 0.93 (0.58–1.43) among IVF women were found for the risk of carcinoma *in situ* (CIS) of the cervix and breast cancer, respectively. When date of conception plus 1 and 3 years were used as start of follow-up, the rate ratios of CIS of the cervix increased to 0.77 (0.57–1.03) and 0.86 (0.60–1.19), respectively, and the corresponding figures for breast cancer decreased to 0.91 (0.58–1.42) and 0.74 (0.40–1.26). CONCLUSION: Following a relatively short follow-up period, there is little if any increased risk of premenopausal cancer development in women who gave birth after IVF treatment. The women who gave birth after IVF treatment had a decreased incidence of CIS of the cervix and breast cancer, but only the former was statistically significant. However, further studies are necessary to include longer follow-up times.

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human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Cancer morbidity in a cohort of 9175 Finnish women treated for infertility

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BACKGROUND: Results of earlier studies on cancer risk in infertile women are inconsistent for many cancer types. Our goal was to study cancer incidence among a cohort of women treated with IVF, including ICSI and frozen embryo transfer (FET), compared with that of a control population.

METHODS: A cohort of women who purchased drugs for IVF (including ICSI and FET treatments, $n = 9175$) in the period 1996–1998 in Finland (later called IVF women) and their age and residence-matched controls further adjusted for socio-economic position and marital status were linked to the Finnish Cancer Registry 1996–2004.

RESULTS: The overall cancer incidence and combined incidence of hormonal-related breast, uterine and invasive ovarian cancers were similar among IVF women and controls. IVF women had statistically significantly less cervical cancer [odds ratio (OR): 0.51, 95% confidence interval (CI): 0.30–0.85], but more skin cancers other than melanoma (OR: 3.11, 95% CI: 1.02–9.6). IVF women had three times more invasive ovarian cancers than controls, but this difference was not statistically significant, possibly due to the small number of cases. IVF women had slightly fewer breast cancers but difference was likewise not statistically significant. All cases of pulmonary cancer were diagnosed among controls ($P = 0.03$).

CONCLUSIONS: General cancer risk or risk of hormonal-related cancers in women was not increased by IVF. The differences in certain cancers suggest a healthy patient effect or may be partly caused by residual socio-economic differences. More large studies and reanalysis of existing studies are needed to evaluate cancer risk among infertile women by subgroups regarding the cause of infertility. When evaluating risk of cancer after drug exposure, dosage and the use of different medicaments should be taken into consideration.

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human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Fertility treatment and cancers—the eternal conundrum: a systematic review and meta-analysis

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STUDY QUESTION: Does fertility treatment (FT) significantly increase the incidence of breast, ovarian, endometrial or cervical cancer?

SUMMARY ANSWER: Overall, FT does not significantly increase the incidence of breast, ovarian or endometrial cancer and may even reduce the incidence of cervical cancer.

WHAT IS KNOWN ALREADY: Infertility affects more than 14% of couples. Infertility and nulliparity are established risk factors for endometrial, ovarian and breast cancer, yet the association with FT is more contentious.

STUDY DESIGN, SIZE, DURATION: A literature search was carried out using Cochrane Library, EMBASE, Medline and Google Scholar up to December 2019. Peer-reviewed studies stating cancer incidence (breast, ovarian, endometrial or cervical) in FT and no-FT groups were identified. Out of 128 studies identified, 29 retrospective studies fulfilled the criteria and were included (n = 21 070 337).

PARTICIPANTS/MATERIALS, SETTING, METHODS: In the final meta-analysis, 29 studies were included: breast (n = 19), ovarian (n = 19), endometrial (n = 15) and cervical (n = 13), 17 studies involved multiple cancer types and so were included in each individual cancer meta-analysis. Primary outcome of interest was cancer incidence (breast, ovarian, endometrial and cervical) in FT and no-FT groups. Secondary outcome was cancer incidence according to specific fertility drug exposure. Odds ratio (OR) and random effects model were used to demonstrate treatment effect and calculate pooled treatment effect, respectively. A meta-regression and eight sub-group analyses were performed to assess the impact of the following variables, maternal age, infertility, study size, outliers and specific FT sub-types, on cancer incidence.

MAIN RESULTS AND THE ROLE OF CHANCE: Cervical cancer incidence was significantly lower in the FT group compared with the no-FT group: OR 0.68 (95% CI 0.46–0.99). The incidences of breast (OR 0.86; 95% CI 0.73–1.01) and endometrial (OR 1.28; 95% CI 0.92–1.79) cancers were not found to be significantly different between the FT and no-FT groups. Whilst overall ovarian cancer incidence was not significantly different between the FT and no-FT groups (OR 1.19; 95% CI 0.98–1.46), separate analysis of borderline ovarian tumours (BOT) revealed a significant association (OR 1.69; 95% CI 1.27–2.25). In further sub-group analyses, ovarian cancer incidence was shown to be significantly higher in the IVF (OR 1.32; 95% CI 1.03–1.69) and clomiphene citrate (CC) treatment group (OR 1.40; 95% CI 1.10–1.77), respectively when compared with the no-FT group. Conversely, the incidences of breast (OR 0.75; 95% CI 0.61–0.92) and cervical cancer (OR 0.58; 95% CI 0.38–0.89) were significantly lower in the IVF treatment sub-group compared to the no-FT group.

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In situ and invasive cervical carcinoma in a cohort of infertile women*

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Objective: To assess the risk of cervical neoplasia associated with the use of ovulation-inducing agents such as clomiphene citrate (CC).

Design: Case-cohort study.

Setting: Infertility clinics in Seattle, Washington.

Patients: A cohort of 3,837 women evaluated for infertility at some time during 1974–1985.

Main Outcome Measure: Computer linkage with a population-based tumor registry was used to identify women diagnosed with cervical cancer before January 1, 1992. Data regarding infertility testing and treatment were abstracted from medical records for women who developed cancer and a randomly selected subcohort.

Results: Thirty-six women in the cohort developed in situ or invasive cervical cancer in comparison with an expected number of 67.8 cases (standardized incidence ratio = 0.5, 95% confidence interval [CI] 0.4 to 0.7). Infertile women with fallopian tube abnormalities were at an increased risk of cervical cancer relative to women whose infertility was believed to be due to other causes. The risk among women who had taken CC was reduced relative to infertile women who had not used this drug (relative risk = 0.4, 95% CI 0.2 to 0.8). This association was present both in women with and without tubal abnormalities. However, the size of the reduction in risk was not influenced by duration of use.

Conclusions: The hypothesis that use of antiestrogenic agents, such as CC, can lead to a reduced risk of cervical neoplasia warrants testing in other studies.

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Συμπεράσματα

- Υπάρχουν αδύναμες/μέτριες ενδείξεις, ότι η θεραπεία γονιμότητας σχετίζεται με τον καρκίνο των ωοθηκών. Δεδομένης της σημαντικής ετερογένειας μεταξύ των μελετών, είναι δύσκολο να προσεγγιστεί το μέγεθος της επίδρασης- ωστόσο, ο συνολικός κίνδυνος είναι πιθανό να είναι μικρός. Επιπλέον, τα στοιχεία υποδηλώνουν ότι τουλάχιστον ένα μέρος αυτού του κινδύνου σχετίζεται με την υποκείμενη ενδομητρίωση, τη γυναικεία υπογονιμότητα ή την ατοκία, που έχουν προηγουμένως συσχετιστεί με αυξημένο κίνδυνο καρκίνου των ωοθηκών.

- Υπάρχουν αδύναμες ενδείξεις, ότι η υποβοηθούμενη αναπαραγωγή, αυξάνει τον κίνδυνο εμφάνισης όγκων ωοθηκών οριακής κακοήθειας.

- Οι περισσότερες μελέτες υψηλής και μέτριας ποιότητας δεν έδειξαν καμία συσχέτιση, ενώ 1 μελέτη μέτριας ποιότητας έδειξε αυξημένο κίνδυνο εμφάνισης καρκίνου του μαστού σε ασθενείς που υποβλήθηκαν σε υποβοηθούμενη αναπαραγωγή.

- Μια μετα-ανάλυση ανέφερε αύξηση του κινδύνου καρκίνου του μαστού που σχετίζεται με παρατεταμένη (>10 κύκλους) χρήση κιτρικής κλομιφαίνης.

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Fertility drugs and cancer: a guideline

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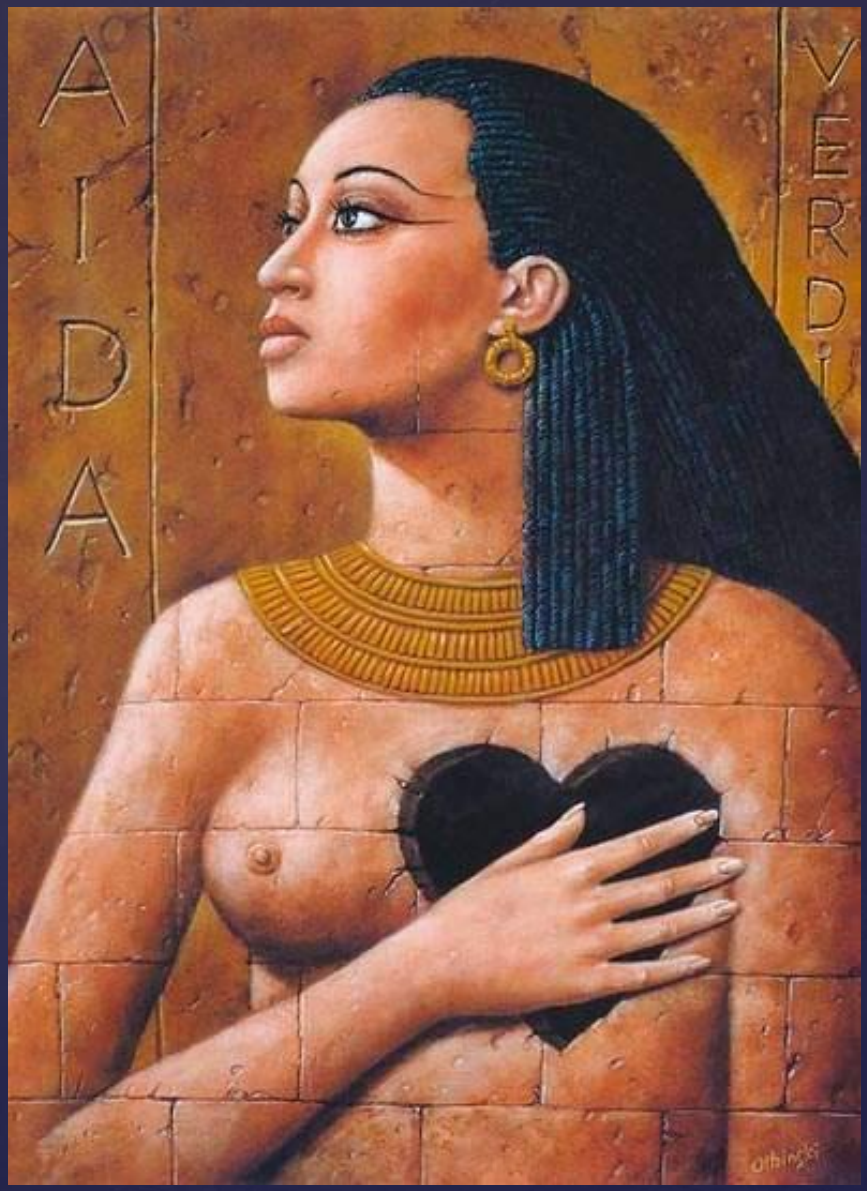
Συμπεράσματα

- Η υποκείμενη υπογονιμότητα αυξάνει τον κίνδυνο καρκίνου του ενδομητρίου. Όταν οι γυναίκες με υπογονιμότητα χρησιμοποιούνται ως μάρτυρες, η χρήση φαρμάκων γονιμότητας δεν σχετίζεται με αυξημένο κίνδυνο καρκίνου του ενδομητρίου.

- Στοιχεία χαμηλής ποιότητας υποδηλώνουν, ότι η έκθεση σε κιτρική κλομιφαίνη ως φάρμακο διέγερσης των ωοθηκών σε γυναίκες με υπογονιμότητα σχετίζεται με αυξημένο κίνδυνο καρκίνου του ενδομητρίου, ιδίως σε αθροιστικές δόσεις >2.000 mg και >7 κύκλους. Αυτό μπορεί να οφείλεται σε μεγάλο βαθμό σε υποκείμενους παράγοντες κινδύνου στις γυναίκες που χρειάζονται θεραπεία με κιτρική κλομιφαινή, όπως το PCOS, παρά στην έκθεση στο ίδιο το φάρμακο. Τα στοιχεία σχετικά με την έκθεση σε γοναδοτροπίνες και τον κίνδυνο καρκίνου του ενδομητρίου ήταν ασαφή.

- Οι περισσότερες μελέτες δεν έδειξαν αυξημένο κίνδυνο καρκίνου του τραχήλου της μήτρας μετά τη χρήση φαρμάκων γονιμότητας-4 μελέτες έδειξαν μειωμένο κίνδυνο.

Ευχαριστώ πολύ!



Αναστασία Μπόθου, Επίκουρη Καθηγήτρια Μαιευτικής