IL RISCHIO ONCOGENO DELLA PMA

Andrea Borini

Outlines

- Infertility: a marker of future cancer risk in women?
- Fertility drugs and cancer:
  - IVF treatment and ovarian cancer / BOT
  - IVF treatment and other gynaecological cancers
  - IVF treatment and other cancer

Infertility: a marker of future health risk in women?

Suneeta Senapati, M.D., M.S.C.E

Division of Reproductive Endocrinology & Infertility, Department of Obstetrics and Gynecology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

A recent meta-analysis of 18 studies including 2,813,481 participants demonstrated a pooled relative risk of all-cause mortality of 1.19 (95% confidence interval [CI] 1.03–1.38) among nulliparous women compared to those with 1 or more live births.

(Zeng et al., Sci Rep 2016)

Abnormal estrogen and progesterone profiles have been implicated in hormone sensitive cancers including breast, ovarian, and endometrial cancer; thus, it is likely that altered profiles observed amongst nulliparous women may be implicated in cancer-related mortality.

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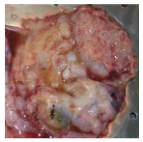
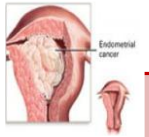
FATTORI DI RISCHIO TUMORI GINECOLOGICI



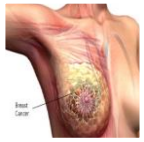
Carcinoma Ovarico

- Età
- Familiarità
- Fattori genetici
- **Nulliparità**
- Menarca precoce
- Menopausa tardiva



Carcinoma Endometriale

- Familiarità
- Menarca precoce
- Menopausa tardiva
- **Nulliparità**
- **Anovularità**
- obesità
- Diabete
- Ipertensione
- Terapia estrogenica
- Terapia con tamoxifene



Carcinoma della mammella

- Età
- Familiarità
- Menarca precoce
- Menopausa tardiva
- **Nulliparità**

PAZIENTE AFFETTA DA INFERTILITA'

Fertility drugs and cancer: a guideline

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

A systematic review of the literature: **113 studies**

SUMMARY

- The data assessing the association between fertility drugs and cancer are limited and principally come from observational studies (Level 2-2 or lower).
- Methodological issues include small sample sizes, heterogeneous treatment regimens, inadequate information about duration and dose of treatment, retrospective analyses, and short follow-up periods.
- Overall, there is fair evidence that women with infertility have an increased risk of breast, ovarian, and endometrial cancer. (Grade B)

Fertility and Sterility® Vol. 106, No. 7, December 2016

FERTILITY DRUGS AND RISK OF CANCER

Study limitations

- use of a non-ideal fertile control population;
- few observations of cancers in the groups studied;
- use of imprecise outcomes such as combining benign and malignant ovarian neoplasms;
- inability to identify the specific medications that were administered or the duration of their use;
- no information regarding dose response;
- no controlling for confounding variables;
- usage and indications for fertility medications have changed since the first associations were reported.

Difficult interpretation of the data

OVARIAN CANCER

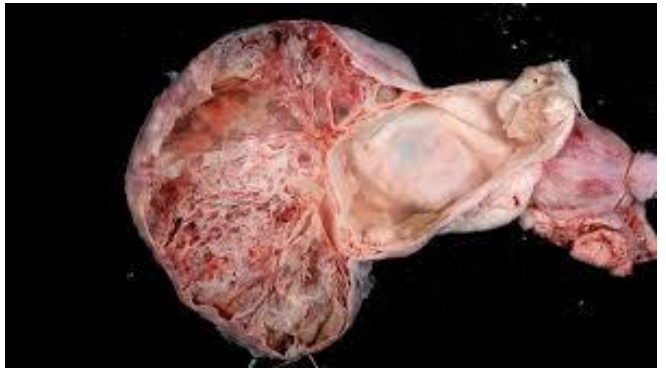
Ovarian cancer is rare and accounts for about 3% of all cancers in women, with approximately 20,000 cases diagnosed annually in the United States.

Parity is inversely related to the risk of ovarian cancer (odds ratio [OR] 0.65, 95% confidence interval [CI] 0.48–0.88).

- Infertility as factor risk of ovarian cancer

The ‘‘incessant ovulation’’ theory suggests that prolonged and uninterrupted years of ovulation increase cancer risk.

• Fertility drugs, which often lead to multiple ovulatory sites within the ovary during a single cycle, are thus hypothesized to increase the risk of ovarian cancer



FERTILITY DRUGS AND RISK OF OVARIAN CANCER

EVIDENCE FROM IN VITRO STUDIES

In vitro studies have demonstrated that approximately half of all ovarian epithelial tumors express gonadotropin receptors.

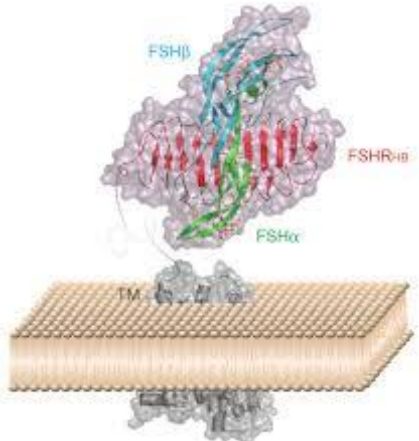
(Mandai M et al., Mol Cell Endocrinol 2007)

FSH, LH, and estradiol stimulate ovarian epithelial cell proliferation and inhibit apoptosis in ovarian epithelial cancer cell lines.

(Stewart SL et al., J Cell Physiol 2004)

Clomiphene citrate potentiates the antiproliferative effect of some chemotherapeutic agents in estrogen receptor–negative ovarian cancer cell lines.

(Kikuchi Y et al., Gynecol Oncol 1993)



FERTILITY DRUGS AND RISK OF OVARIAN CANCER

In vitro fertilization and risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi Healthcare Services

Louise A. Brinton, Ph.D.,[a] Britton Trabert, Ph.D.,[a] Varda Shalev, M.D.,[b,c] Eitan Lunenfeld, M.D., M.H.A.,[d] Tal Sella, M.D.,[b,d] and Gabriel Chodick, Ph.D.[b,d]

Retrospective cohort study

87,403 women treated for infertility

Age 18-45 yrs

Hazard ratios (HRs) for specific cancers

Adjusted hazard ratios for breast and gynecologic cancers associated with fertility treatments.

	Cases, n	Person-years	HR[a]	95% CI
Ovarian				
No fertility treatment	11	137,074	1.00	reference
Any fertility treatment	34	564,275	0.90	(0.45–1.79)
IVF	21	186,918	1.58	(0.75–3.29)
1–3 cycles	10	105,736	1.40	(0.59–3.32)
≥4 cycles	11	81,182	1.78	(0.76–4.13)
GnRH analogues	11	173,641	0.93	(0.40–2.16)
Clomiphene	20	425,227	0.75	(0.36–1.58)
Progestogen	23	449,283	0.77	(0.37–1.60)

Brinton LA et al., Fertil Steril 2013

FERTILITY DRUGS AND RISK OF OVARIAN CANCER

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]

Population based cohort study.

54 362 women with infertility problems

Effect of four groups of fertility drugs on overall risk of ovarian cancer

Median follow-up of 16 years

Variables	Adjusted rate ratio (95% CI)			
	Gonadotrophins*	Clomifene citrate	hCG	GnRH
Use:				
Never	1.00	1.00	1.00	1.00
Ever	0.83 (0.50 to 1.37)	1.14 (0.79 to 1.64)	0.89 (0.62 to 1.29)	0.80 (0.42 to 1.51)
No of cycles:				
1-4	0.74 (0.41 to 1.33)	1.27 (0.83 to 1.94)	0.96 (0.62 to 1.48)	0.81 (0.42 to 1.56)
5-9	1.09 (0.49 to 2.44)	1.03 (0.57 to 1.86)	0.86 (0.47 to 1.57)	0.68 (0.09 to 5.38)
≥10	0.96 (0.09 to 10.30)	0.92 (0.42 to 2.02)	0.70 (0.28 to 1.80)	—
Time since first use (years):				
<5	0.67 (0.29 to 1.54)	0.80 (0.32 to 1.99)	0.78 (0.35 to 1.75)	0.72 (0.28 to 1.89)
5-9	1.12 (0.58 to 2.21)	1.48 (0.80 to 2.73)	1.22 (0.67 to 2.23)	0.99 (0.43 to 2.33)
10-14	0.80 (0.29 to 2.18)	0.99 (0.53 to 1.87)	0.83 (0.43 to 1.62)	0.60 (0.13 to 2.70)
≥15	0.44 (0.06 to 3.14)	1.18 (0.70 to 1.99)	0.78 (0.43 to 1.42)	—

Jensen A et al, BMJ, 2009

9.baby FAMILY AND FERTILITY CENTER

Cochrane Library 2013

Cochrane Database of Systematic Reviews

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

Rizzuto I, Behrens RF, Smith LA

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.

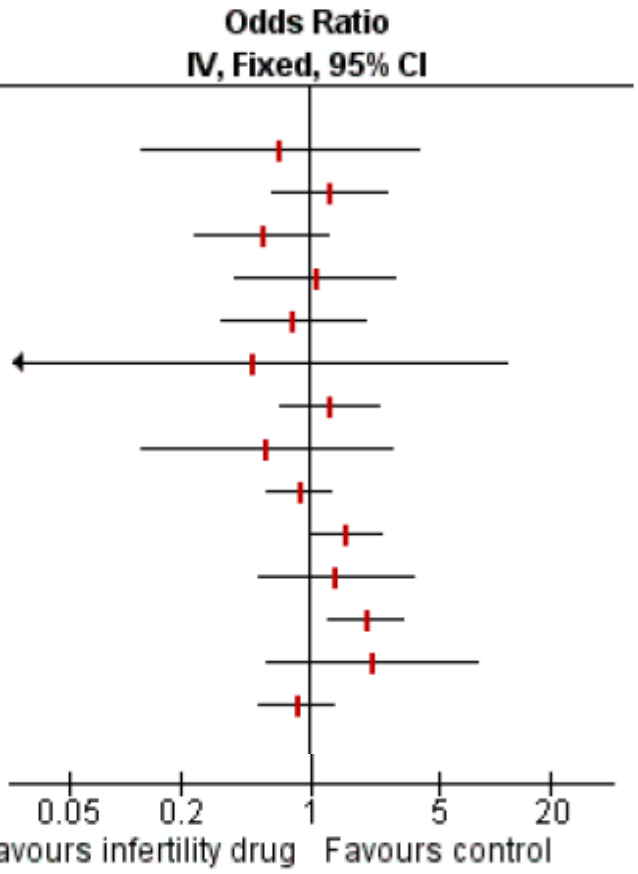
There was no evidence of an increased risk in women exposed to clomiphene alone or clomiphene plus gonadotrophin, compared with unexposed women. One case-control study reported an increased risk in users of human menopausal gonadotrophin (HMG)(OR 9.4, 95% CI 1.7 to 52). However, this estimate is based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

Authors' conclusions

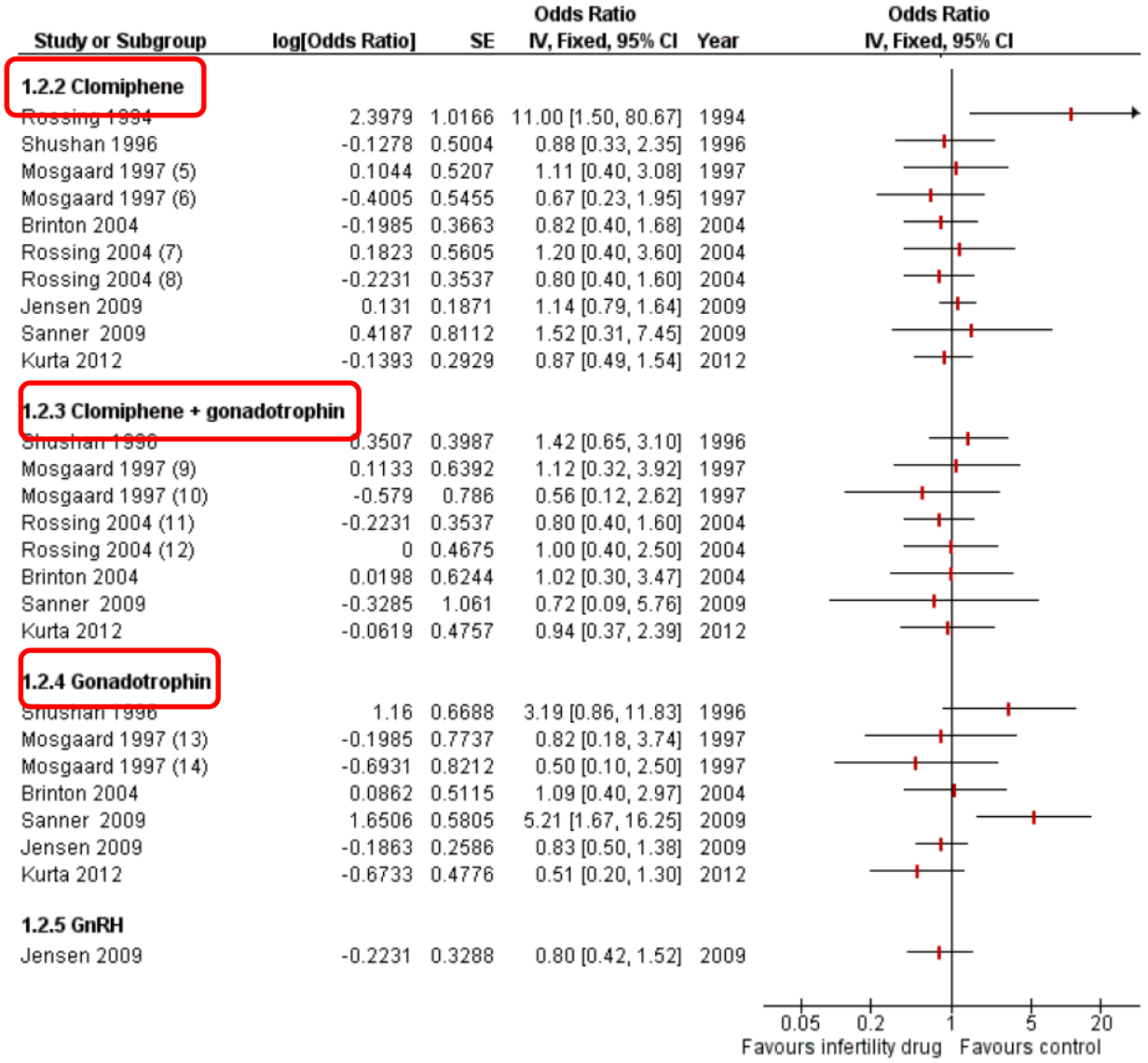
We found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. There may be an increased risk of borderline ovarian tumours in subfertile women treated with IVF. Studies showing an increase in the risk of ovarian cancer had a high overall risk of 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.

Forest plot of comparison: Infertility drugs versus no infertility drug
Outcome: Invasive ovarian cancer

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI	Year
1.2.1 Any infertility drug				
Franceschini 1994	-0.3567	0.8961	0.70 [0.12, 4.05]	1994
Shushan 1996	0.27	0.3735	1.31 [0.63, 2.72]	1996
Mosgaard 1997 (1)	-0.5798	0.4323	0.56 [0.24, 1.31]	1997
Parazzini 1997	0.0953	0.5161	1.10 [0.40, 3.02]	1997
Mosgaard 1997 (2)	-0.1863	0.4586	0.83 [0.34, 2.04]	1997
Potashnik 1999	-0.6931	1.6423	0.50 [0.02, 12.50]	1999
Parazzini 2001	0.2624	0.3158	1.30 [0.70, 2.41]	2001
Doyle 2002	-0.5276	0.8126	0.59 [0.12, 2.90]	2002
Rossing 2004 (3)	-0.1054	0.2069	0.90 [0.60, 1.35]	2004
Rossing 2004 (4)	0.47	0.2398	1.60 [1.00, 2.56]	2004
Dos Santos Silva 2009	0.3507	0.5028	1.42 [0.53, 3.80]	2009
Kallen 2011	0.7372	0.2422	2.09 [1.30, 3.36]	2011
Yli-Kuha 2012	0.8109	0.683	2.25 [0.59, 8.58]	2012
Kurta 2012	-0.1393	0.2433	0.87 [0.54, 1.40]	2012



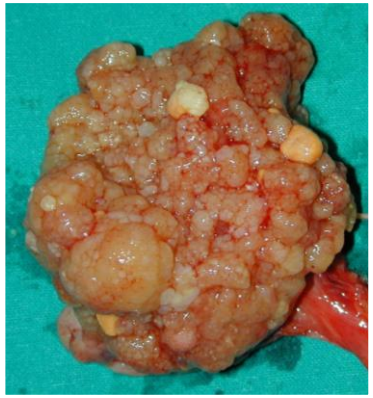
Forest plot of comparison: Infertility drugs versus no infertility drug
Outcome: Invasive ovarian cancer

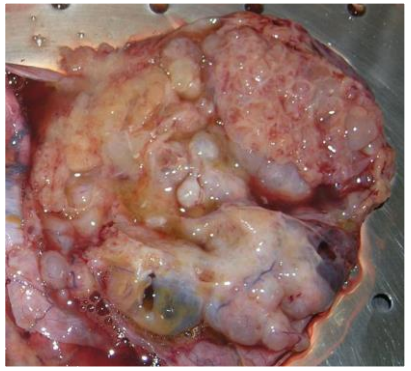


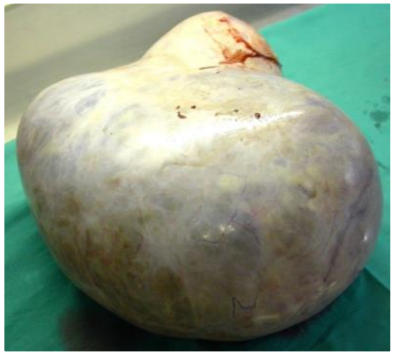
BORDERLINE OVARIAN TUMORS (BOT)

10-15% of epithelial ovarian neoplasms

In contrast to invasive ovarian cancer, borderline ovarian tumors are indolent in their disposition, are more likely to be diagnosed in women of reproductive age, and have a favorable prognosis with more than 95% of women surviving 5 years beyond diagnosis.







While there is very little support for an association between fertility drug use and invasive ovarian cancer, several studies have shown **a link between fertility drugs and borderline ovarian tumors**

FERTILITY DRUGS AND RISK OF BORDERLINE OVARIAN TUMORS

In vitro fertilization is associated with an increased risk of borderline ovarian tumours

Louise M. Stewart [a,*], C D'Arcy J. Holman [a], Judith C. Finn [b,c], David B. Preen [a], Roger Hart [d,e]

Population cohort study.

21639 women infertility treatment or investigation

All hospitals in Western Australia

Age 20-44 years

	All women in the cohort	Women not undergoing IVF	Women undergoing IVF
	21,639	14,095	7544
diagnosis of borderline ovarian tumour	31	14	17

The rate of borderline ovarian tumors in women undergoing IVF was higher with an HR of 2.46 (95% CI 1.20–5.04), which translates into 11 additional cases of borderline tumors per 10,000 women.

Potential borderline ovarian tumour risk and protective factors.

Exposure	Number in exposed group	Crude (unadjusted) HR (95% CI)[a]	Adjusted HR (95% CI)[b]
IVF	7544	2.48 (1.22–5.04)	2.46 (1.20–5.04)
Birth[c]	14,902	0.70 (0.34–1.43)	0.89 (0.43–1.88)
Age at first birth			
No birth recorded	6737	1.00	1.00
Age<30 at first birth	7047	0.41 (0.15–1.13)	0.62 (0.20–1.87)
Age≥30 at first birth	7855	1.01 (0.46–2.21)	1.05 (0.48–2.34)
High socio-economic status[d]	5268	0.46 (0.16–1.30)	0.36 (0.12–1.03)

Stewart LM et al., Gynecol Oncol 2013

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

Rizzuto I, Behrens RF, Smith LA

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.

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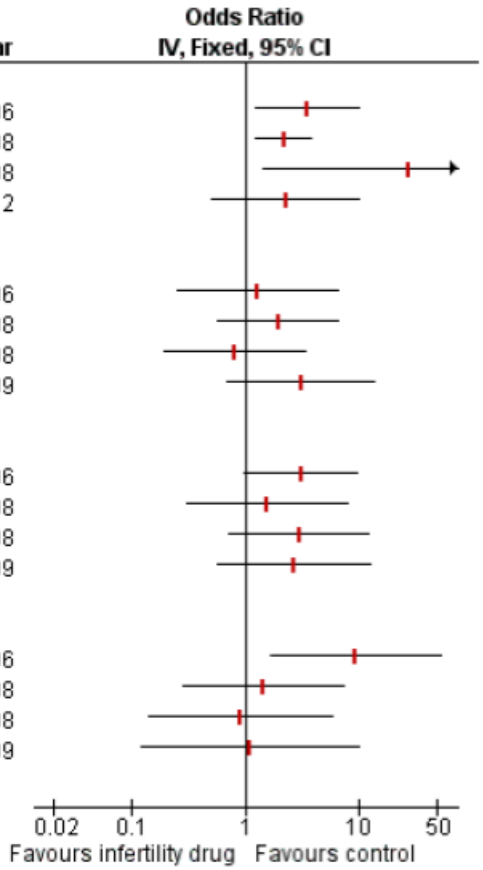
Authors' conclusions

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.

Forest plot of comparison: Infertility drugs versus no infertility drug
Outcome: borderline ovarian cancer

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI	Year
1.1.1 Any infertility drug				
Shushan 1996	1.2585	0.5365	3.52 [1.23, 10.07]	1996
Mosgaard 1998 (1)	0.7839	0.2902	2.19 [1.24, 3.87]	1998
Parazzini 1998	3.3143	1.4957	27.50 [1.47, 515.85]	1998
Yli-Kuha 2012	0.8109	0.7639	2.25 [0.50, 10.06]	2012
1.1.2 Clomiphene				
Shushan 1996	0.2469	0.8333	1.28 [0.25, 6.55]	1996
Mosgaard 1998 (2)	0.6575	0.6313	1.93 [0.56, 6.65]	1998
Mosgaard 1998 (3)	-0.2231	0.7335	0.80 [0.19, 3.37]	1998
Sanner 2009	1.1184	0.76	3.06 [0.69, 13.57]	2009
1.1.3 Clomiphene + gonadotrophin				
Shushan 1996	1.1249	0.5843	3.08 [0.98, 9.68]	1996
Mosgaard 1998 (4)	0.4318	0.8346	1.54 [0.30, 7.91]	1998
Mosgaard 1998 (5)	1.1019	0.7228	3.01 [0.73, 12.41]	1998
Sanner 2009	0.9933	0.7847	2.70 [0.58, 12.57]	2009
1.1.4 Gonadotrophin				
Shushan 1996	2.2386	0.8836	9.38 [1.66, 53.01]	1996
Mosgaard 1998 (6)	0.3577	0.832	1.43 [0.28, 7.30]	1998
Mosgaard 1998 (7)	-0.0943	0.955	0.91 [0.14, 5.91]	1998
Sanner 2009	0.1044	1.13	1.11 [0.12, 10.17]	2009



Fertility drugs and cancer: a guideline

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Summary statements:

Grade B	Based on the available data, we can be reasonably reassured **that there is no meaningful increased risk of invasive ovarian cancer** following the use of fertility drugs in infertile women.
Grade B	Based on the available data there is fair evidence that the risk of invasive ovarian cancer is not different with one fertility drug compared with another.
Grade C	While several studies have shown **a small increase in the absolute risk of borderline ovarian tumors after fertility treatments**, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors.
Grade C	There is insufficient evidence to recommend against the use of fertility medications to avoid borderline ovarian tumors.

IVF and BREAST CANCER

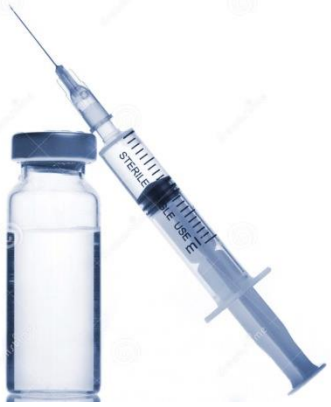
One unifying theory for breast cancer development suggests that exposure to endogenous estrogen (earlier menarche, later menopause) increases risk.

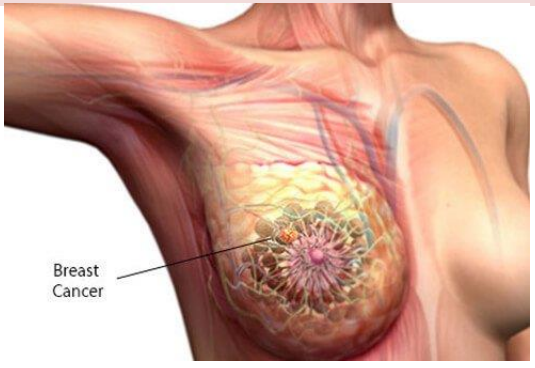
(Yager JD et al., NEJM 2006)

The data regarding the association of progesterone exposure and breast cancer are contradictory. While progesterone is protective to the endometrium, it appears to be mitogenic to the breast. However, parity, a state of high progesterone levels, is associated with a lower risk of breast cancer.

(Bernstein et al., Cancer Epidemiol Biomarkers Prev 1995)

Fertility drugs → higher estrogen and progesterone
Therefore has been postulated to be associated with an increase in breast cancer, especially with prolonged use.





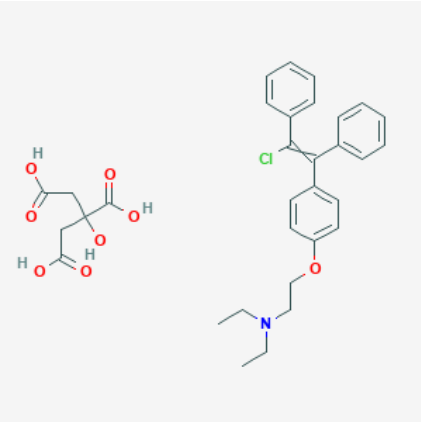
CLOMIPHENE CITRATE

Clomiphene citrate is structurally and functionally similar to tamoxifen, and when administered continuously, tamoxifen lowers the risk of breast cancer.

(Levine M et al., CMAJ 2001)

Clomiphene citrate causes apoptosis in breast cancer cell lines in vitro.

(Lavie et al., Int J Cancer 1998)



FERTILITY DRUGS AND RISK OF BREAST CANCER

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

Lerner-Geva Liat[1,3], Rabinovici Jaron[2,3], Olmer Liraz[1], Blumstein Tzvia[1], Mashiach Shlomo[2,3] & Lunenfeld Bruno[4]

Retrospective cohort study.

2.431 women treated for infertility

Follow up for more than 20 years

No excess risk following exposure to ovulation induction was observed in both univariate and multivariate analyses.

Breast cancer incidence according to diagnosis of infertility, presence of estrogen and progesterone and treatment with ovulation induction.

	N	Observed	Expected	SIR	95% CI
Diagnosis of infertility					
Hormonal	1340	70	72.8	0.96	0.75–1.22
Nonhormonal	1061	83	59.1	1.4	1.12–1.74
Presence of estrogen and progesterone					
Estrogen+progesterone–	935	54	48.4	1.11	0.84–1.45
Estrogen+progesterone+	671	47	37.4	1.26	0.92–1.67
Estrogen–progesterone–	129	3	7.92	0.38	0.08–1.11
Treatment with ovulation induction					
CC+hMG	238	12	12.9	0.93	0.48–1.63
CC	884	54	44.7	1.21	0.91–1.58
hMG	159	4	9.9	0.4	0.11–1.6
No treatment	1150	83	64.4	1.29	1.03–1.6

CC, clomiphene citrate; hMG, human menopausal gonadotrophin; SIR, standardized incidence ratios.

Lerner-Geva L et al., Gynecol Endocrinol 2012

FERTILITY DRUGS AND RISK OF BREAST CANCER

Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study

Ronald T. Burkman, M.D.,[a] Mei-Tzu C. Tang, Ph.D.,[b] Kathleen E. Malone, Ph.D.,[b] Polly A. Marchbanks, Ph.D.,[c] Jill A. McDonald, Ph.D.,[c] and Suzanne G. Folger, Ph.D.[c]

Multicenter case-control study.

4,575 patients with primary invasive breast cancer

Aged 35-64 years

Risk of breast cancer and use of fertility medications.

Characteristics	All women: Cases (n = 4,566), N (%)	All women: Controls (n = 4,676), N (%)	All women: OR[a] (95% CI)	Women diagnosed with infertility: Cases (n = 227), N (%)	Women diagnosed with infertility: Controls (n = 266), N (%)	Women diagnosed with infertility: OR[a] (95% CI)
Fertility drug use						
Never	4,382 (96.0)	4,476 (95.7)	1.0	121 (53.3)	145 (54.5)	1.0
Ever	184 (4.0)	200 (4.3)	0.9 (0.8–1.2)	106 (46.7)	121 (45.5)	1.2 (0.8–1.7)
Duration of use						
<6 mo	74 (1.6)	77 (1.7)	1.0 (0.7–1.4)	31 (13.7)	34 (12.8)	1.2 (0.7–2.2)
≥6 mo	110 (2.4)	121 (2.6)	0.9 (0.7–1.2)	75 (33.0)	86 (32.5)	1.2 (0.8–1.8)
Type of fertility drug[b]						
hCG	23 (0.5)	21 (0.5)	1.2 (0.6–2.1)	15 (6.6)	16 (6.0)	1.5 (0.7–3.4)
Duration of use (mo)						
<6	11 (0.3)	11 (0.2)	1.1 (0.5–2.5)	7 (3.1)	9 (3.4)	1.8 (0.6–5.4)
≥6	11 (0.3)	9 (0.2)	1.3 (0.5–3.0)	8 (3.6)	6 (2.3)	2.2 (0.7–7.0)
Cycles of use (n)						
<6	13 (0.3)	15 (0.3)	0.9 (0.4–1.9)	9 (4.0)	11 (4.1)	1.8 (0.7–4.8)
≥6	9 (0.2)	6 (0.1)	1.5 (0.5–4.3)	6 (2.6)	5 (1.9)	2.0 (0.5–7.3)
Clomiphene citrate	141 (3.1)	145 (3.1)	1.0 (0.8–1.3)	85 (37.4)	91 (34.2)	1.4 (0.9–2.1)
Duration of use (mo)						
<6	58 (1.3)	56 (1.2)	1.1 (0.7–1.5)	29 (12.8)	27 (10.2)	1.7 (0.9–3.2)
≥6	83 (1.8)	87 (1.9)	1.0 (0.7–1.3)	56 (24.7)	63 (23.7)	1.3 (0.8–2.2)
Cycles of use (n)						
<6	69 (1.5)	67 (1.4)	1.1 (0.8–1.5)	37 (16.3)	36 (13.5)	1.7 (0.9–3.0)
≥6	69 (1.5)	75 (1.6)	1.0 (0.7–1.3)	45 (19.8)	53 (19.9)	1.2 (0.7–2.0)
hMG	38 (0.8)	28 (0.6)	1.5 (0.9–2.4)	25 (11.0)	24 (9.0)	1.7 (0.9–3.3)
Duration of use (mo)						
<6	16 (0.4)	17 (0.4)	1.0 (0.5–2.0)	8 (3.5)	14 (5.3)	1.2 (0.5–3.3)
≥6	22 (0.5)	11 (0.2)	2.1 (1.0–4.4)[b]	17 (7.5)	10 (3.8)	2.8 (1.1–6.8)[b]
Cycles of use (n)						
<6	22 (0.5)	19 (0.4)	1.2 (0.7–2.3)	13 (5.7)	15 (5.6)	1.7 (0.7–4.1)
≥6	15 (0.3)	6 (0.1)	2.7 (1.0–6.9)[b]	11 (4.8)	6 (2.3)	3.8 (1.2–11.8)[b]
Other fertility drug[c]	18 (0.4)	25 (0.5)	0.8 (0.4–1.4)	16 (7.1)	17 (6.4)	1.5 (0.7–3.3)
Duration of use (mo)						
<6	7 (0.2)	15 (0.3)	0.5 (0.2–1.2)	6 (2.6)	9 (3.4)	1.5 (0.5–4.7)
≥6	11 (0.2)	9 (0.2)	1.3 (0.5–3.1)	10 (4.4)	7 (2.6)	2.4 (0.8–7.0)
Cycles of use (n)						
<6	10 (0.2)	18 (0.4)	0.6 (0.3–1.3)	9 (0.4)	12 (4.5)	1.5 (0.6–4.1)
≥6	7 (0.2)	7 (0.2)	1.1 (0.4–3.0)	6 (2.6)	5 (1.9)	2.0 (0.5–7.2)

Although this study found no association of risk related to use of clomiphene, there was some indication of a risk elevation among women with long-term use of menopausal gonadotrophins.

Use for at least 6 or more months or at least six cycles was associated with RR ranging from 2.7–3.8.

FERTILITY DRUGS AND RISK OF BREAST CANCER

IVF and breast cancer: a systematic review and meta-analysis

Theodoros N. Sergentanis[1], Andreas-Antonios Diamantaras[1], Christina Perlepe[1], Prodromos Kanavidis[1], Alkistis Skalkidou[2] and Eleni Th. Petridou[1,*]

Based on available data, we can be reasonably reassured that there is no meaningful increased risk of invasive ovarian cancer following the use of fertility drugs in infertile women. (Grade B)

Table II Results of the meta-analysis examining the association between IVF and breast cancer.

	n[a]	Effect estimate (95% CI)	P	Heterogeneity I^2, P*
Approach preferring[b] estimates which excluded the first year of follow-up after IVF				
Analysis versus general population	6	0.91 (0.74–1.11)[R]	0.341	51.0%, 0.070
Subanalysis on SIRs	4	0.99 (0.73–1.34)[R]	0.935	53.1%, 0.094
Subanalysis on ORs	2	**0.78 (0.65–0.94)**	0.009	0.0%, 0.600
Analysis versus infertile women	3	1.02 (0.88–1.18)	0.800	0.0%, 0.427
Subanalysis on HRs	2	1.00 (0.85–1.18)	0.967	33.1%, 0.221
Subanalysis on IRRs	1	1.10 (0.77–1.56)	0.605	NC
Approach preferring[b] estimates derived from the total follow-up				
Analysis versus general population	6	0.92 (0.75–1.13)[R]	0.450	51.3%, 0.068
Subanalysis on SIRs	4	1.00 (0.84–1.18)	0.972	52.0%, 0.100
Subanalysis on ORs	2	**0.79 (0.66–0.95)**	0.014	0.0%, 0.387
Analysis versus infertile women	3	1.02 (0.88–1.18)	0.784	0.0%, 0.435
Subanalysis on HRs	2	1.01 (0.86–1.18)	0.950	31.8%, 0.226
Subanalysis on IRRs	1	1.10 (0.77–1.56)	0.605	NC

Human Reproduction Update, Vol.20, No.1 pp. 106–123, 2014

FERTILITY DRUGS AND RISK OF ENDOMETRIAL CANCER

Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort

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

Retrospective cohort study.

12,193 women evaluated for infertility

Follow up for an average of 26 years

	Endometrial cancer (n = 118)	Non-cases (n = 9714)	HR[a]	95% CI
Never use of clomiphene	66	6010	1.00	Referent
Ever use	52	3704	1.39	0.96–2.01
Never use of gonadotrophins	104	8774	1.00	Referent
Ever use	14	940	1.34	0.76–2.37
Combination of clomiphene and gonadotrophins				
Neither	66	5833	1.00	Referent
Clomiphene only	38	2941	1.24	0.83–1.86
Gonadotrophins only	0	177	NC[c]	NC[c]
Both	14	763	1.77	0.98–3.19

Brinton LA et al., Hum Reprod 2013

FERTILITY DRUGS AND RISK OF ENDOMETRIAL CANCER

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

Lerner-Geva Liat[1,3], Rabinovici Jaron[2,3], Olmer Liraz[1], Blumstein Tzvia[1], Mashiach Shlomo[2,3] & Lunenfeld Bruno[4]

Retrospective cohort study.

2.431 women treated for infertility

Follow up for more than 20 years

The incidence of endometrial cancer following treatment with either CC or human menopausal gonadotropin (hMG) was not increased compared with the general population, while treatment with CC and hMG was associated with an increased risk

Endometrial cancer incidence according to diagnosis of infertility, presence of estrogen and progesterone and treatment with ovulation induction.

	N	Observed	Expected	SIR	95% CI
Diagnosis of infertility					
Hormonal	1340	19	9.38	2.02	1.22–3.16
Nonhormonal	1061	11	8.37	1.31	0.66–2.35
Presence of estrogen and progesterone					
Estrogen+progesterone–	935	13	6.11	2.13	1.13–3.64
Estrogen+progesterone+	671	8	5.31	1.51	0.65–2.97
Estrogen–progesterone–	129	1	1.11	0.9	0.01–5.01
Treatment with ovulation induction					
CC+hMG	238	8	1.6	5.0	2.15–9.85
CC	884	6	5.62	1.07	0.39–2.33
hMG	159	3	1.39	2.16	0.43–6.32
No treatment	1150	13	9.15	1.42	0.76–2.43

CC, clomiphene citrate; hMG, human menopausal gonadotrophin; SIR, standardized incidence ratios.

Lerner-Geva L et al., Gynecol Endocrinol 2012

Fertility drugs and cancer: a guideline

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Summary statements:

Grade B

There is fair evidence that fertility drugs are not associated with an increased risk of breast cancer.

Grade B

Overall, there is fair evidence that fertility drugs are not associated with an increased risk of endometrial cancer.

FERTILITY DRUGS AND RISK OF OTHER CANCER

THYROID CANCER

Six studies → conflicting results:

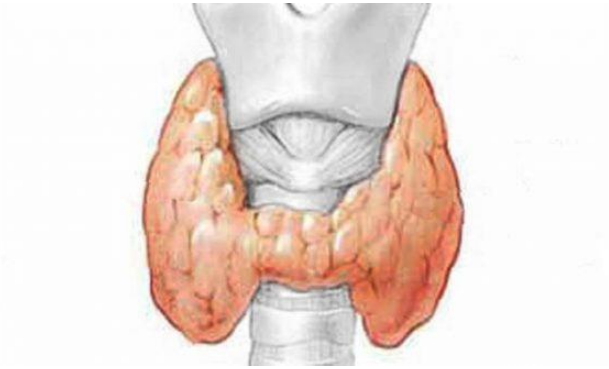
<u>Two largest studies:</u> non significant increase in the incidence of thyroid cancer :

- Use of Clomiphene citrate: RR 1.42 (95% CI 0.5– 3.7) (which did not vary with dose or duration of therapy)
- Use of gonadotropins: no effect (RR 1.1, 95% CI 0.2–4.9)

(Althuis MD, et al. . Am J Obstet Gynecol 2005)

- Use of CC: HR 1.57 (95% CI 0.89–2.75) based on 55 patients

(Brinton LA et al., Fertil Steril 2015).



FERTILITY DRUGS AND RISK OF OTHER CANCER

Fertility drugs and cancer: a guideline

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Summary statements:

Grade B	Overall, there is fair evidence that fertility drugs are not associated with an increased risk of invasive thyroid cancer.
Grade C	Overall, there is insufficient evidence that fertility drugs are associated with an increased r of melanoma.
Grade B	Overall, there is fair evidence that fertility drugs are not associated with an increased risk colon cancer.
Grade C	Based on a single study, there is insufficient evidence that fertility drugs are associated with an increased risk of lymphoma.
Grade B	Overall, there is fair evidence that fertility drugs are not associated with an increased risk of cervical cancer.

Conclusions

- The data assessing the association between fertility drugs and cancer are limited and principally come from observational studies (Level 2-2 or lower).
- There is fair evidence that women with infertility have an increased risk of breast, ovarian, and endometrial cancer. (Grade B)
- However, use of fertility drugs does not appear to increase this risk.

9.baby: il primo network italiano dedicato alla fertilità

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15 CENTRI IN TUTTA ITALIA

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