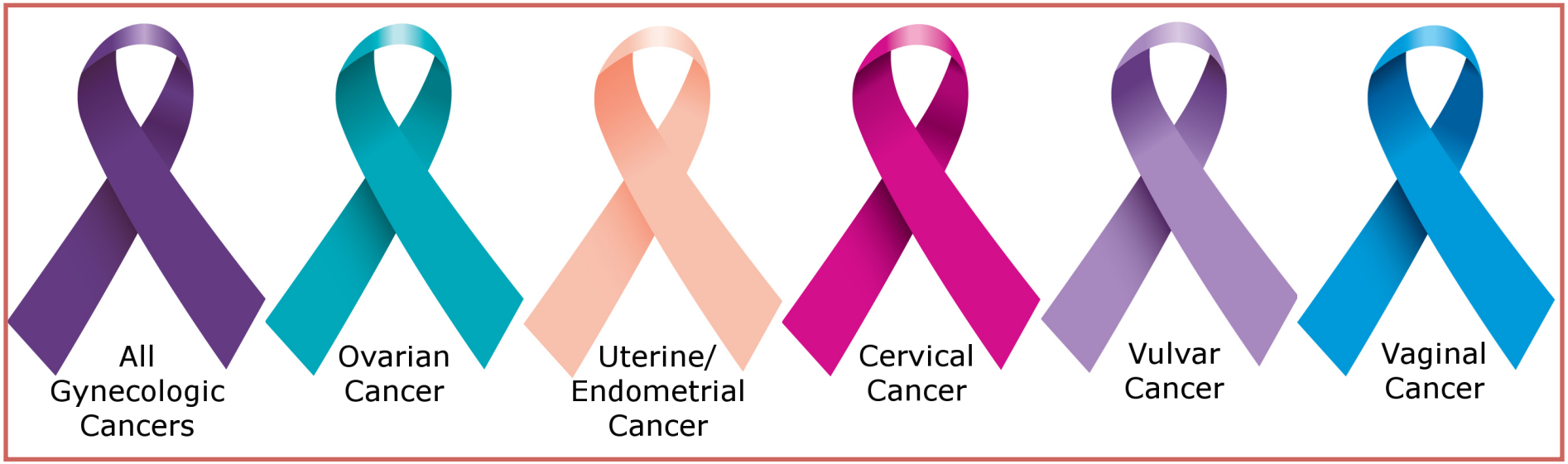

Φάρμακα Υποβοηθούμενης Αναπαραγωγής και καρκίνος

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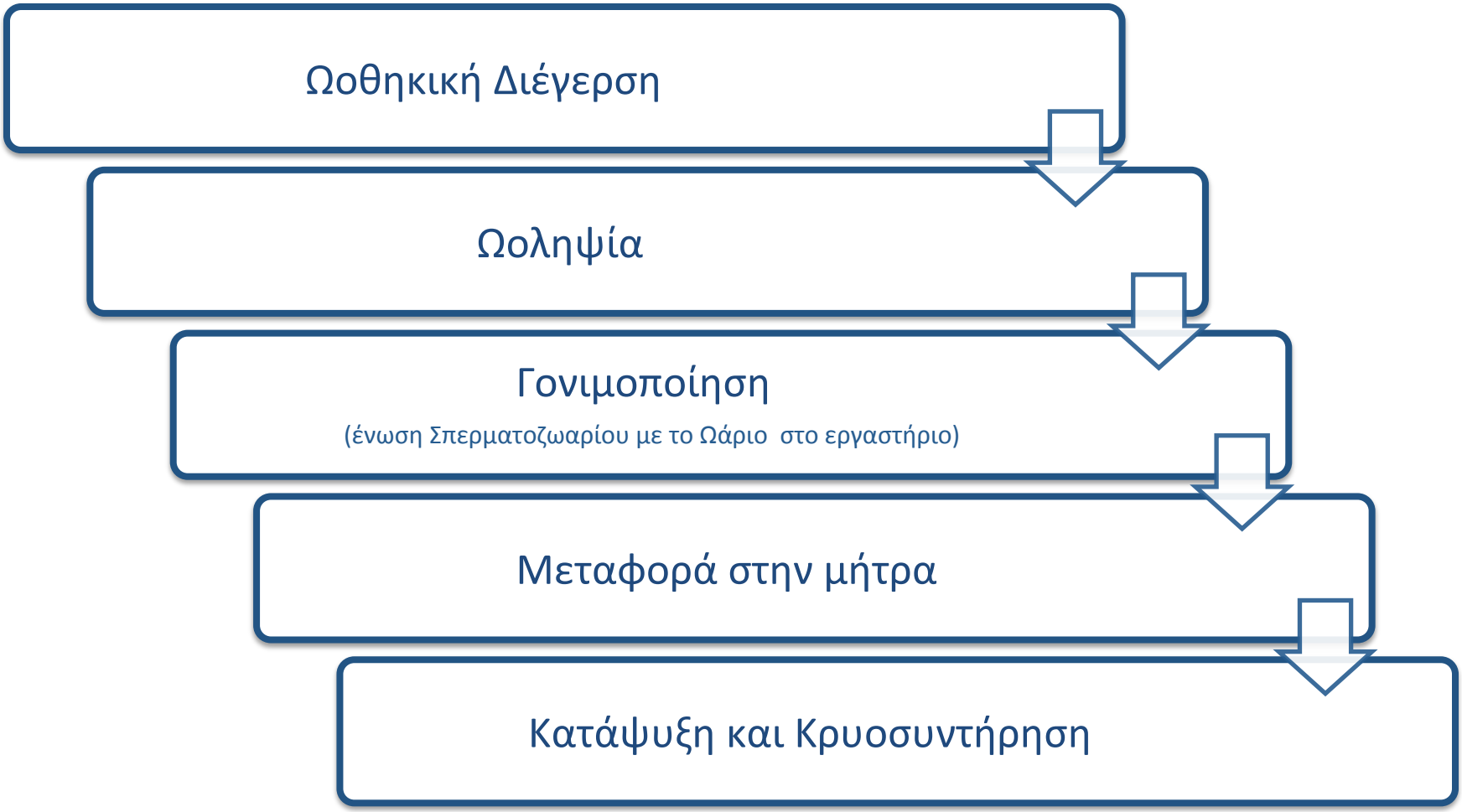
Fertility drugs and Cancer

- ✓ Ovarian stimulation + IUI
- ✓ Ovarian stimulation for IVF

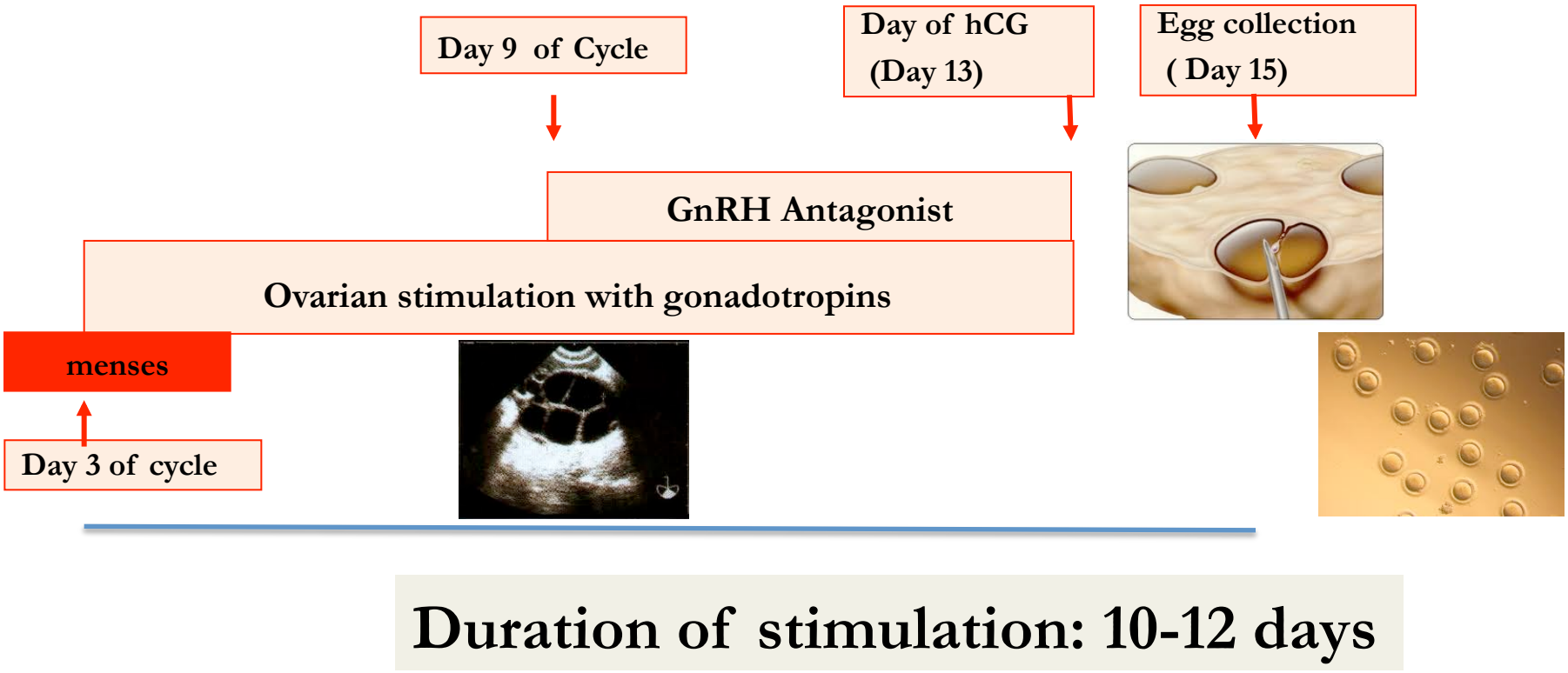
- GnRH analogs
- Gonadotropins (HMG)
- Clomifene citrate (CC)
- hCG

- Ovarian cancer
- Breast cancer
- Endometrial cancer
- Other cancers

Εξωσωματική Γονιμοποίηση

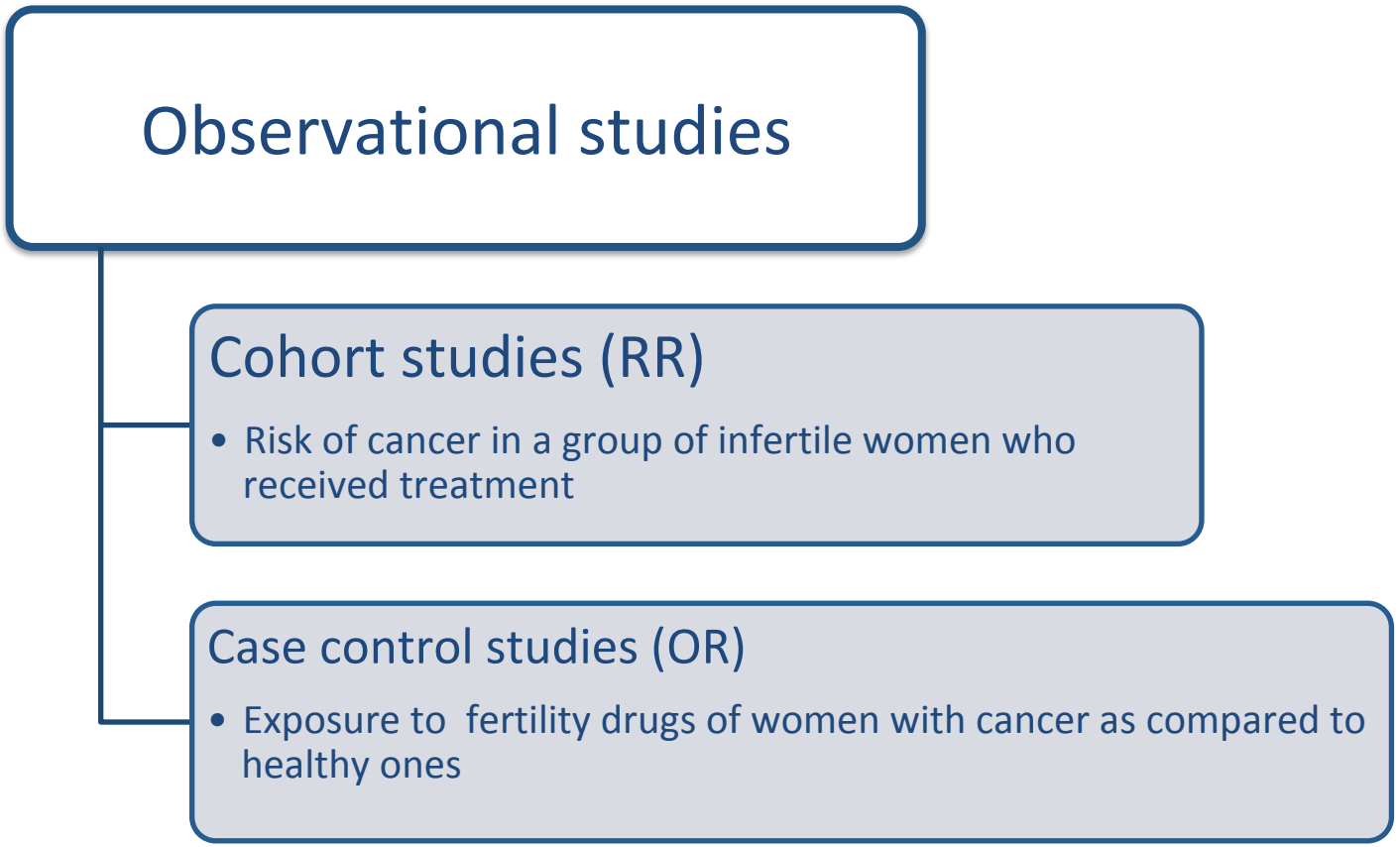


Ovarian stimulation



Duration of stimulation: 10-12 days

Fertility drugs and Cancer



Fertility drugs and Cancer

- **What are we looking for?**
  - Risk of cancer in infertile women who received drugs as compared to the general population.

  (SIR: Standarized Incidence Ratio)
  - Risk of cancer in infertile women who received treatment as compared to those who did not (Cohort studies RR: relative risk)
  - Exposure to fertility drugs of women with cancer as compared to healthy ones

  (Case control studies: OR: odds ratio)

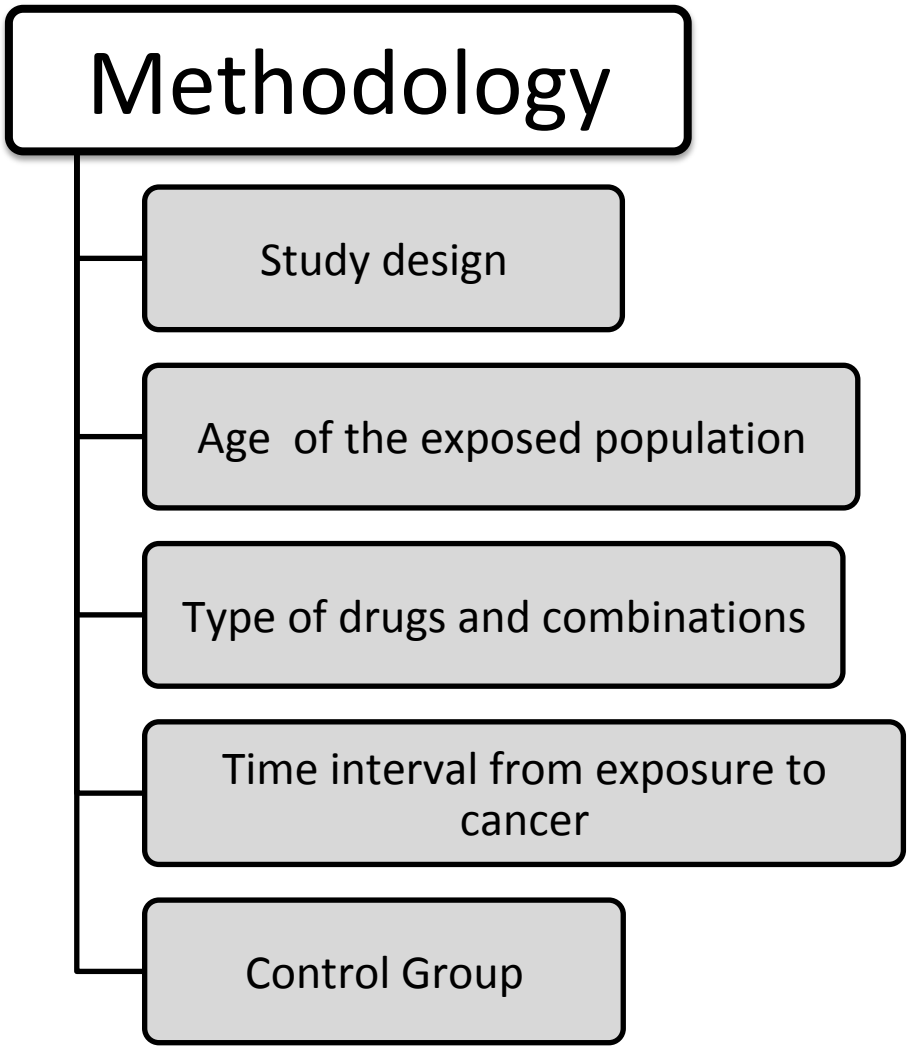
What is the right question?

Risk of cancer in the infertile women vs all women?

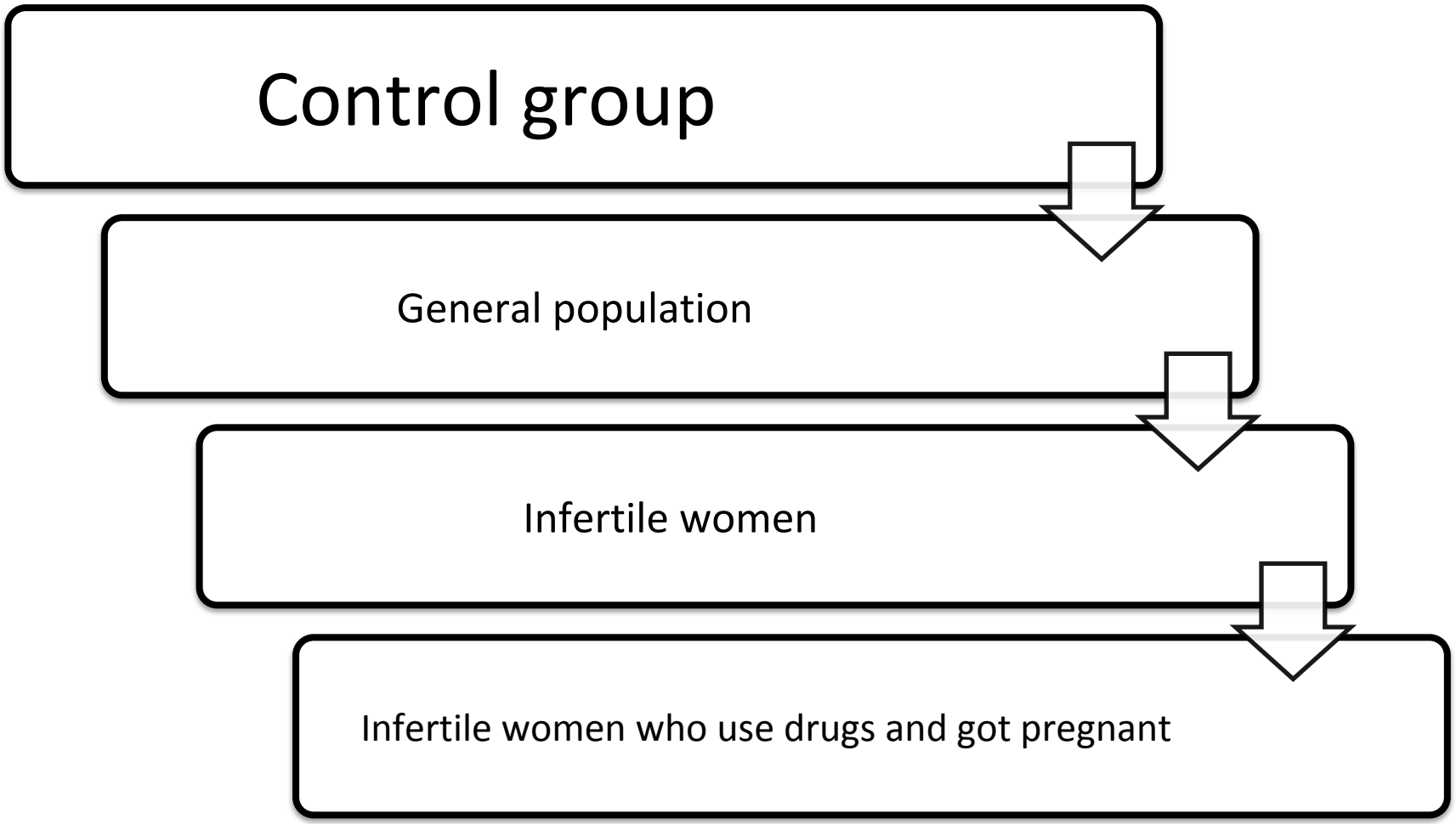
Risk of cancer in the infertile women that were treated with fertility medications vs the ones not treated with?

Risk of cancer of infertile women who conceived after treatment vs the one who did not conceive?

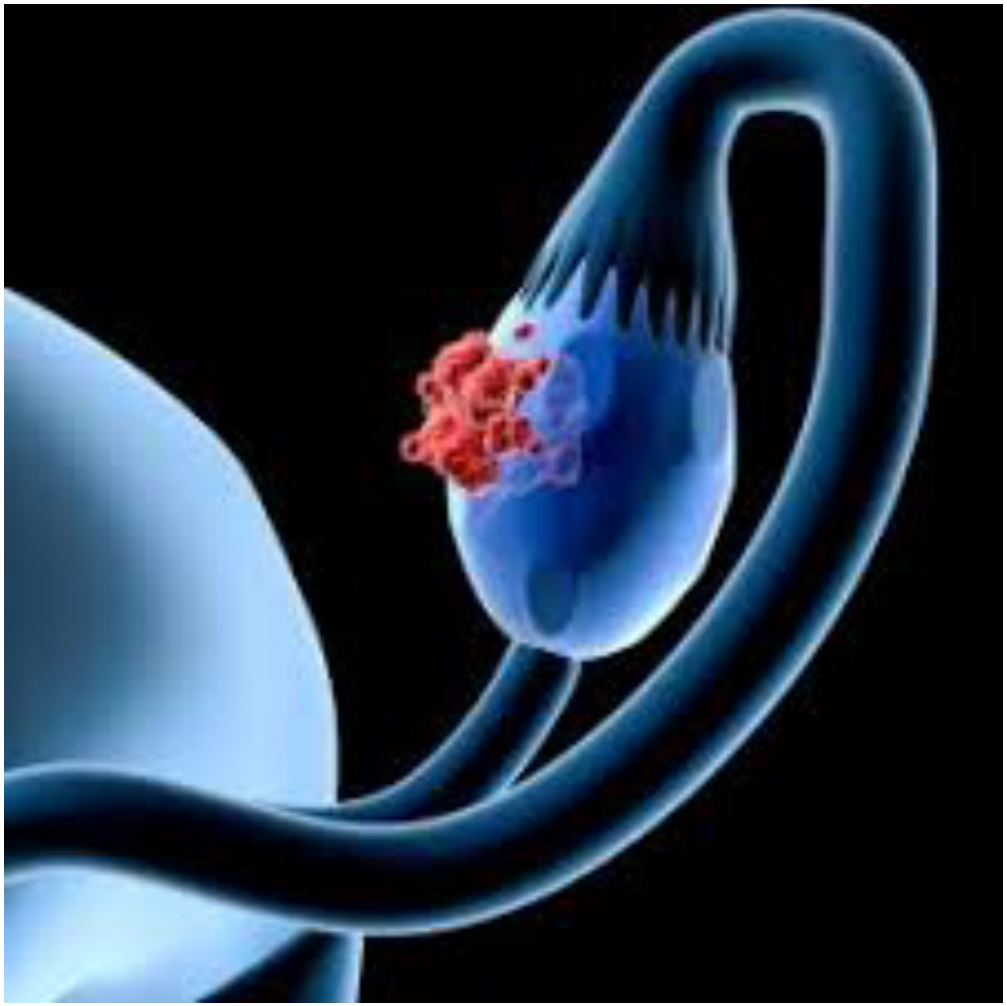
Fertility drugs and Cancer



Fertility drugs and Cancer



Ovarian cancer



Fertility Drugs and Ovarian Cancer

Whittemore et al. Am J Epidemiol 1992; 136: 1204-1211)

Metanalysis of 12 case-control studies:

Women who received fertility drugs had 27 x higher risk of ovarian cancer

- Small detail:

  Treated but not pregnant: OR: 27 (CI, 2.3-315)

  Treated and pregnant: OR: 1.4 (0.5-3.6)

Ovarian Cancer

- Rossing et al. NEJM 1994;331:771-6
  - 3837 women treated for infertility (1974-1985)
  - 11 tumors : SIR 4,4 (95% CI, 1.3-4,5)
    - 5 borderline tumors

Clomiphene citrate	RR vs non users
No	1
Yes	2.3 (0.5-11.4)
1-11	0.8 (0.1-5.7)
≥12	11.1(1.5-82.3)

Ovarian Cancer

Cohort studies

Author	Size	SIR (95% CIs):		RR (95% CI): within cohort	
Rossing et al. 1992	3,837	No drug	1.4 (0.2–5.0)	CC	2.3 (0.5–11.4)
		CC	3.1 (1.4–5.9)	≥12 cycles	11.1 (1.5–82.3)
		hMG/FSH	5.6 (0.1–31.0)	hCG	1.0 (0.2–4.3)
		hCG	2.8 (0.6–8.0)		
Modan et al. 1998	2,496	No treatment	1.6 (0.6–3.5)		
		Treatments	1.7 (0.6–3.8)		
		CC	2.7 (0.9–5.8)		
Venn et al. 1999	29,666	No IVF	1.2 (0.5–2.6)		
		IVF	0.9 (0.4–1.8)		

Ovarian Cancer

Cohort studies

Author	Size	SIR (95% CIs):		RR (95% CI): within cohort	
Klip et al. 2002	23,592	No IVF	1.4 (0.4–3.2)	IVF	0.4 (0.1–1.2)
		IVF	1.4 (0.7–2.6)		
		≥7 cycles	1.8 (0.0–9.8)		
Doyle et al. 2002	5,556	No treatment	1.7 (0.2–6.0)	Treatment	0.6 (0.1–3.0)
		Treatment	0.8 (0.2–2.2)		
Brinton et al. 2004	12,193	No CC	2.1 (1.4–3.0)	CC	0.8 (0.4–1.5)
		CC	1.8 (1.0–3.0)	≥15 years F/U	1.5 (0.7–3.2)
		No hMG	2.0 (1.4–2.7)	hMG	1.1 (0.4–2.8)
		hMG	2.3 (0.7–5.3)	≥15 years F/U	2.5 (0.7–8.3)

Fertility drugs, reproductive strategies and ovarian cancer risk

JOR JOURNAL OF OVARIAN RESEARCH

Table 1 Fertility drugs and ovarian cancer (Cohort studies)

Study	Treatments	Population	Results
Rossing et al. [21] 1994	Clomiphene citrate	3837 women, 9 ovarian cancer in exposed, 2 ovarian cancer in unexposed	≥ 12 cycles with clomiphene citrate associated with RR = 11.1 (95% CI: 1.5-82.3) compared to the general population
Potashnik et al. [25] 1999	Definited as use of fertility drugs	1197 women. 1 ovarian cancer in exposed; 1 ovarian cancers in unexposed	SIR in exposed = 0.68 (95% CI: 0.01-3.80). SIR in unexposed = 1.35 (95% CI: 0.02-7.49).
Doyle et al. [23] 2002	Clomiphene citrate, hMG, hCG, GnRH analog,	4188 women, 4 ovarian cancers in exposed, 2 ovarian cancers in unexposed	SIR in exposed = 0.84 (95% CI: 0.23-2.15). SIR in unexposed = 1.67 (95% CI: 0.20-6.05). RR exposed vs unexposed = 0.59 (95% CI: 0,12-3,00)
Brinton et al. [26] 2004	Clomiphene citrate or gonadotropins	12193 infertile women, 15 ovarian cancers in exposed, 30 cancers in unexponed	RR exposed vs unexposed = 0.82 (95% CI: 0.4-1.5)
Calderon-Margalit et al. [24] 2009	Self reported exposure to fertility drugs	15030 parous women. Only 1 cancer in exposed 42 cancers in unexposed	No association found between fertility drugs and ovarian cancer (age-adjusted HR = 0.61). Only parous women
Jensen et al. [28] 2009	hMG, FSH, Clomiphene citrate, hCG, GnRH-analog,	54362 women, 156 ovarian cancers, 58 ovarian cancers in exposed, 98 cancers in unexponed	No risk increase associated with hMG, FSH, hCG, GnRH-analog. RR exposed vs unexposed for Clomiphene citrate: 1.14 (95% CI: 0.79- 1.64)
Dos Santos Silva et al. [29] 2009	Definited as use of fertility drugs	7355 women 12 cancers in exposed, 8 cancers in unexposed	SIR in exposed =1.10 (95% CI: 0,57-1.93) SIR in unexposed =0,78 (95% CI: 0.34-1.53) RR exposed vs unexposed =1,42 (95% CI: 0,53-3.99)
Sanner et al. [22] 2009	Clomiphene citrate and/or gonadotropins	2768 women, 16 cancers in exposed (9 ovarian cancers, 7 borderline tumors); 13 cancers in unexposed	SIR = 5.89 for ovarian cancer (95% CI: 1.91-13.75) SIR = 3.61 for borderline tumors (95% CI: 1.45-7.44). RR = 5.28 (95% CI: 1.70-16.47) for invasive cancers associated with gonadotropins
Lerner-Geva et al. [35] 2012	Gonadotropins	2431 women, 18 ovarian cancer cases, 30 years of follow-up	SIR = 1.0 (95% CI: 0.59-1.57)
Trabert et al. [27] 2013	Clomiphene citrate, with or without gonadotropins	9825 women, 85 ovarian cancers	RR for clomiphene citrate = 1.34 (95% CI: 0.86-2.07) RR for gonadotropins = 1.00 (95% CI: 0.48-2.08)

Abbreviations: RR = relative risk, *CI* = confidence interval, *SIR* = standardized index ratio, *hMG* = human menopausal gonadotropin, *hCG* = human chorionic gonadotropin, *GnRH* = gonadotropin releasing hormone, *HR* = hazard ratio, *FSH* = follicle stimulating hormone.

JOR JOURNAL OF OVARIAN RESEARCH

Table 2 IVF and ovarian cancer (Cohort studies)

Study	Treatments	Population	Results
Venn et al. [44] 1995	IVF	29666 women, 3 cancers in exposed, 3 cancers in unexposed	SIR in exposed = 1.7 (CI 95%: 0.55-5.27) SIR in unexposed = 1.62 (95% CI: 0.52-5.02) RR exposed vs unexposed = 1,45 (95% CI: 0.28-7.55)
Venn et al. [45] 1999	IVF	29700 women, 7 ovarian cancers in exposed, 6 in unexposed	SIR in exposed = 0,88 (95% CI: 0,42- 1.84) SIR in unexposed = 1.16 (95% CI: 0.52-2.59)
Dor et al. [47] 2002	IVF	Retrospective cohort of 5026 women, 1 ovarian cancer case	SIR in exposed = 0.57 (95% CI: 0.01-3.20)
Klip et al. [48] 2002	IVF	23592 women, 17 ovarian cancers	No differences in risk exposed vs unexposed Detailed information obtained through questionnaires and from medical records
Lerner Geva et al. [43] 2003	IVF	1082 women, 3 ovarian cancers	SIR in exposed = 5.0 (95% CI: 1.02-14.6) SIR = 1.67 (0.02-9.27) when cancers developing within 1 year were excluded No untreated group Registry match
Kallen et al. [46] 2011	IVF	24058 women, 26 ovarian cancers	RR exposed vs unexposed = 2.09 (95% CI: 1,39-3.12)
van Leeuwen et al. [49] 2011	IVF	19146 IVF women, 6006 subfertile women not treated with IVF	Risk of borderline ovarian tumours increased in the IVF group compared with the general population. SIR = 1.76 (95% 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. SIR = 3.54 (95% CI: 1.62-6.72) after 15 years.
Yli-kuha et al. [50] 2013	IVF	9175 women, 9 invasive ovarian cancers, 4 borderline ovarian tumors	OR for invasive cancers = 2.57 (95% CI: 0.69-9.23) OR for borderline tumors = 1.68 (95% CI: 0.31-9.27)
Brinton et al. [51] 2013	IVF	87403 women, 45 ovarian cancers	Global HR =1.58 (95% CI: 0.75-3.29), HR among women receiving ≥ 4 IVF cycles =1.78 95% CI: 0.76-4.13).

Abbreviations: IVF = in vitro fertilization, *SIR* = standardized index ratio, *CI* = confidence interval, *RR* = relative risk, *OR* = odds ratio, *HR* = hazard ratio.

Ovarian Cancer
Case control studies

Author	Cases	Controls	Comparison	OR (95% CI)
Shu et al. 1989	229 (2.6)	229 (0.4)	FDs vs. no use	2.1 (0.2–22.7)
Whittemore et al. 1992	718 (2.8)	1,236 (0.9)	FDs vs. no infertility	2.8 (1.3–6.1)
			Nulligravids	27.0 (2.3–316)
			Gravids	1.4 (0.5–3.6)
Francheski et al. 1994	195 (1.0)	1,339 (1.1)	FDs vs. no use	0.7 (0.2–3.3)
Shushan et al. 1996	164 (12)	408 (7.1)	FDs vs. no use	1.3 (0.6–278)
			Clomiphene	0.9 (0.3–2.3)
			hMG	3.2 (0.9–11.8)

Ovarian Cancer

Author	Cases	Controls	Comparison	OR (95% CI)
Mosgaard et al. 1997	684 (20.7)	1,721 (23.8)	FDs vs. no use (nulliparous women)	0.8 (0.4–2.0)
			Clomiphene	0.7 (0.2–2.0)
			hMG/hCG	0.8 (0.2–3.7)
Parazzini et al. 1997	971 (0.5)	2,758 (0.4)	FDs vs. no use	1.1 (0.4–3.3)
			≥6 cycles	1.0 (0.2–3.8)
Parazzini et al 2001	1,031 (1.5)	2,411 (1.1)	FDs vs. no use	1.3 (0.7–2.5)
Ness et al. 2002	1,060 (14.1)	1,337 (15.0)	FDs vs. no use (sub-fertile women)	1.0 (0.8–1.3)
			Nulligravids	1.75 (0.7–4.2)
			Gravids	0.7 (0.5–1.0)

FD= Fertility drugs

Use of fertility drugs and risk of ovarian cancer: results from a US-based case-control study

Michelle L. Kurta[1], Kirsten B. Moysich[2], Joel L. Weissfeld[1,3], Ada O. Youk[1,4], Clareann H. Bunker[1], Robert P. Edwards[3,5], Francesmary Modugno[1,3,5], Roberta B. Ness[6], and Brenda Diergaarde[1,3,*]

A total of 902 cases were enrolled. Controls, N=1802, were frequency matched to cases (~2:1) by 5-year age group and telephone area code

- ✓ Among all 2704 HOPE participants, 152 (5.6%) women reported ever using fertility drugs.
- ✓ Ever use of fertility drugs was not significantly associated with ovarian cancer risk in the total HOPE population (OR: 0.93, 95%CI: 0.65–1.35), nor was duration of use (never compared to <6 months of use, OR: 1.05, 95%CI: 0.61–1.80; never compared to ≥6 months of use, OR: 0.82, 95%CI: 0.50–1.34),
- ✓ Adjusting for the same covariates, no significant associations between ovarian cancer risk and ever use of fertility drugs were observed when separately evaluating borderline (OR: 0.64, 95%CI: 0.26–1.55) and invasive tumors (OR: 1.02, 95%CI: 0.69–1.50).

Cancer Epidemiol Biomarkers Prev. 2012 August ; 21(8): 1282–1292.

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A total of 902 cases were enrolled. Controls, N=1802, were frequency matched to cases (~2:1) by 5-year age group and telephone area code

- ✓ In the group that seek fertility treatment (N=447) Use of fertility drugs was reported by 148 (33%)
- ✓ **Ever use of fertility drugs was not significantly associated with ovarian cancer** risk and remained non-significant after additional adjustment for cause of infertility (OR: 0.66, 95%CI: 0.36–1.22), age medical attention was sought (OR: 0.86, 95%CI: 0.53–1.40),
- ✓ Additionally, **no significant associations** between ever use of fertility drugs and ovarian cancer risk were observed when **separately assessing borderline** (OR: 0.96, 95%CI: 0.31–2.94; adjusted for age, duration of OC use, talc, and age at menarche) **and invasive tumors** (OR: 0.85, 95%CI: 0.52–1.39; adjusted for all covariates identified by stepwise regression).

Cancer Epidemiol Biomarkers Prev. 2012 August ; 21(8): 1282–1292.

Cochrane Library

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

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

For borderline ovarian tumours, exposure to any fertility drug was associated with a two to three-fold increased risk in two case-control studies.

Authors' conclusions

We found no convincing evidence of an increase in the risk of invasive ovarian tumors with fertility drug treatment.

WILEY

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.

Types of infertility and risk of ovarian cancer

- ✓ 12,193 women evaluated for infertility (1965-1988)
- ✓ 8,429 women available for analysis
- ✓ Median F/U 18.8 years with more than 80% had at least 15 years of F/U

Objective of the study:

- ✓ Risk of ovarian cancer compared to the general population
- ✓ Risk of ovarian cancer in relation to type of infertility

Brinton L.A. F&S 2004

Types of infertility and ovarian cancer

- Infertile women have double the risk for developing ovarian cancer (SIR=1,98 95% CI,1.4-2.6)

	Primary infertility	Secondary infertility
	SIR (95% CI)	SIR (95% CI)
Endometriosis	4.19 (2.0-7.7)	1.05 (0.2-3.1)
Anovulation	1.65 (0.4-4.2)	2.12(0.9-4.2)
Pelvic/Tubal	3.24 (1.6-6)	1.27 (0.5-2.8)
Male	2.66 (1.1-5.5)	1.12 (0.2-3.3)
Cervical	1.56 (0.0-8.7)	1.14 (0.0-6.4)
Uterine	2.48 (0.5-7.2)	1.97 (0.4-5.8)

Brinton L.A. F&S 2004

Endometriosis and Ovarian Cancer

Histologic type	Number of patients	Presence of endometriosis
All types	**79**	**22 (28%)**
Endometrioid	**23**	**9 (39%)**
Clear Cell	**17**	**7 (41%)**
Mixed	**8**	**4 (50%)**

La Cuesta et. al. Gyn Onc.60,238-244 (1996)

Endometriosis and Ovarian Cancer

Patients with endometriosis

Histology	No.of patients	Total (%)	Atypical
Clear cell	43	30 (69.8)	25
Endometrioid	7	3 (42.9)	2
Serous	60	4 (8.0)	2
Mucinous	17	0 (0.0)	0
Total	127	37 (29.1)	29

Ogawa et.al. Gyn. Onc 77,298-304 (2000)

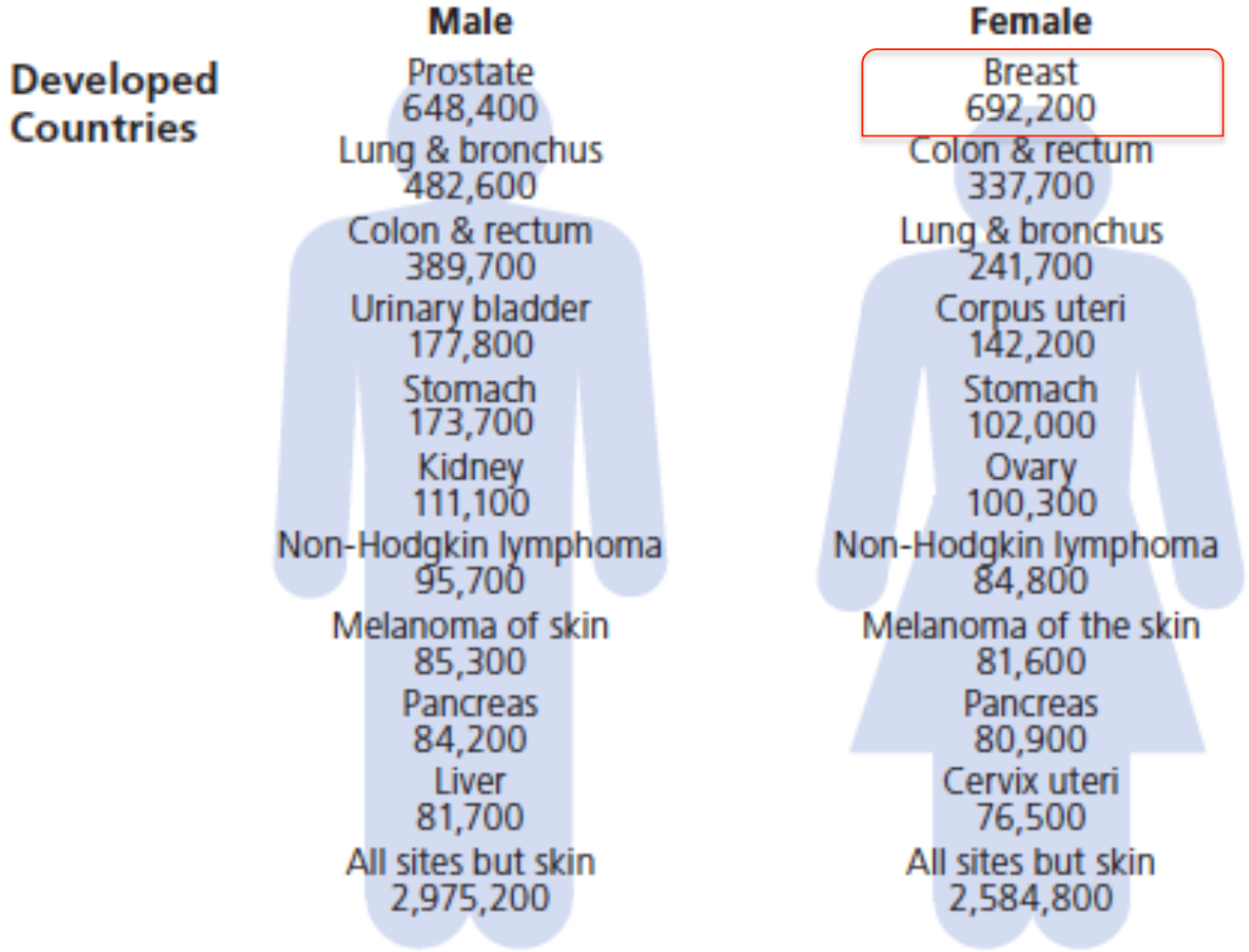
Endometriosis and ovarian cancer

- Mutations in the genes that encode for metabolic and detoxification enzymes, such as GALT and GSTM, have been implicated in the pathogenesis of endometriosis and in the progression to carcinoma of the ovary.
- PTEN, a tumor suppressor gene commonly mutated in endometriosis, is found mutated in endometrioid carcinoma of the ovary, but not in other forms of ovarian cancer.
- Somatic mutations in the PTEN gene were identified in 20% of endometrioid carcinomas and 20.6% of solitary endometrioid ovarian cysts.

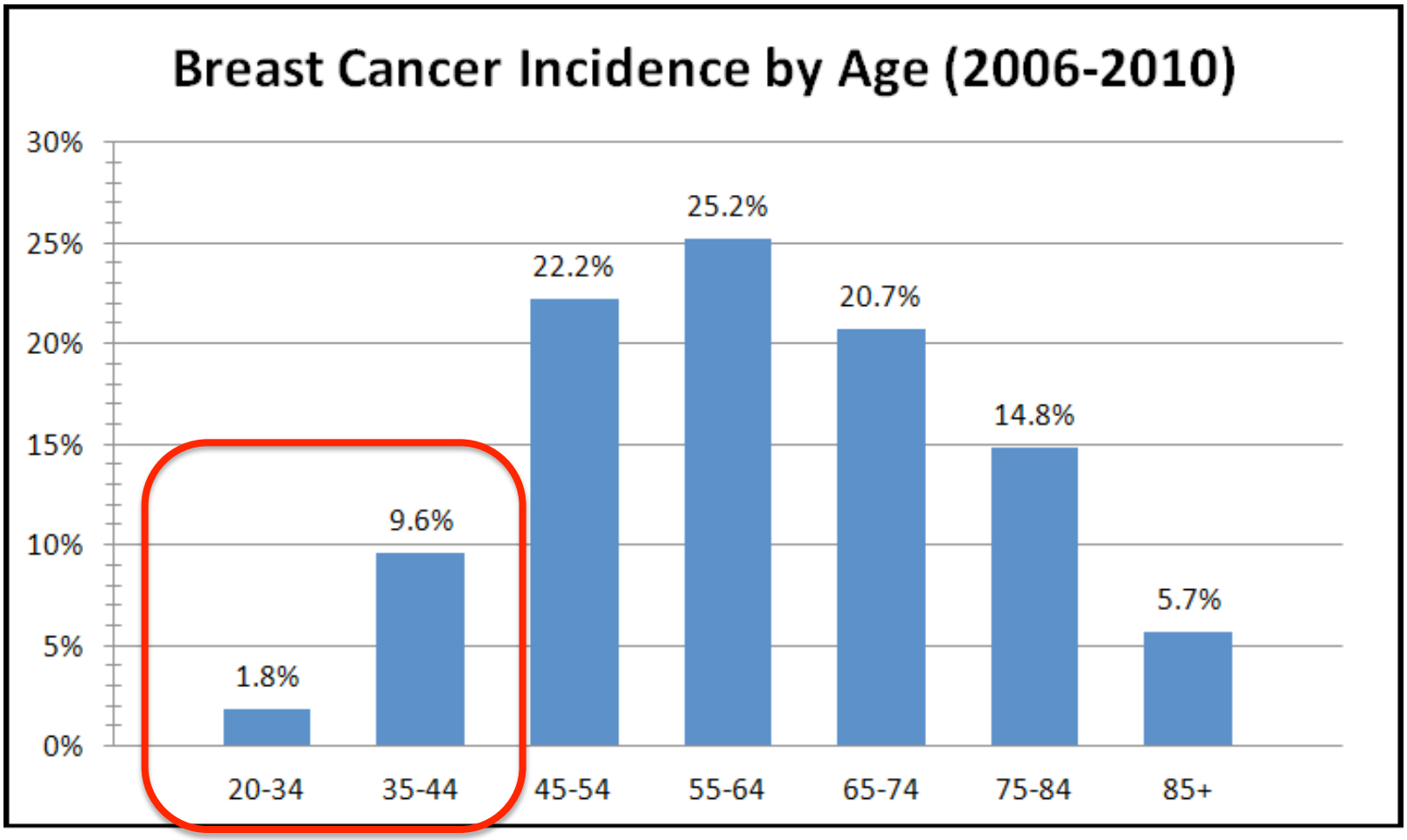
Swiersz LM. Ann NY Acad Sci 2002 Mar ;955:281-92

Breast Cancer

Estimated New Cancer Cases for Leading Cancer Sites



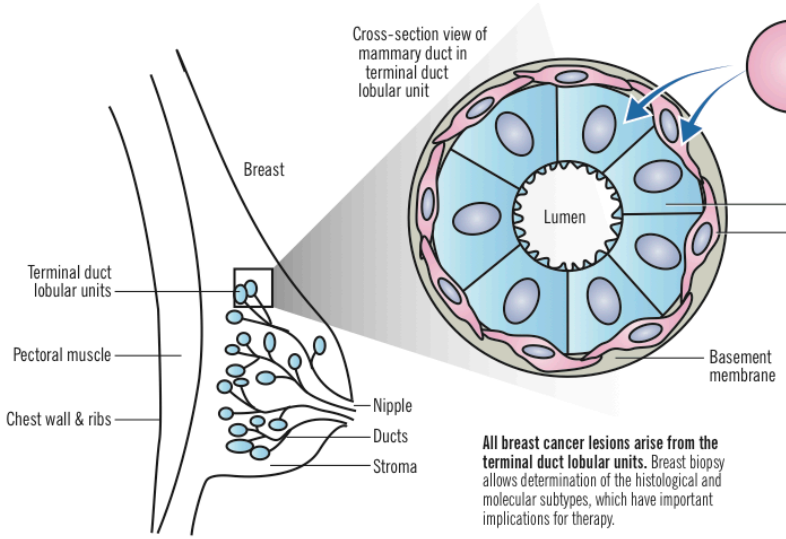
Breast cancer age distribution.



National Cancer Institute

Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jenna Rebelo



All breast cancer lesions arise from the terminal duct lobular units. Breast biopsy allows determination of the histological and molecular subtypes, which have important implications for therapy.

Normal breast stem cells or progenitor cells transform into breast cancer cells. The cancer cells are similar in phenotype to the normal basal and luminal cells of the ductal structure.

Basal or myoepithelial cells
- Contractile cells for milk ejection
- *Estrogen receptor* –
- Progesterone receptor –

Luminal or epithelial cells
- Respond to hormonal stimulation for milk production
- *Estrogen receptor* +
- Progesterone receptor +/–

Cancer cell phenotype

Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	**Ductal carcinoma in situ (DCIS)** 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	**Lobular carcinoma in situ (LCIS)** 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	**Invasive ductal carcinoma (IDC)** 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	**Invasive lobular carcinoma (ILC)** 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

Molecular subtypes	Triple negative ER–, PR–, HER2–	HER2+	Luminal B	Luminal A
% of breast cancers	15-20%	10-15%	20%	40%
Receptor expression		HER2		ER+/PR+
Histologic grade Level of cell differentiation		High (grade III)		Low (grade I)
Prognosis Correlates to histologic grade		Poor		Good
Response to medical therapy		Chemotherapy Trastuzumab		Endocrine

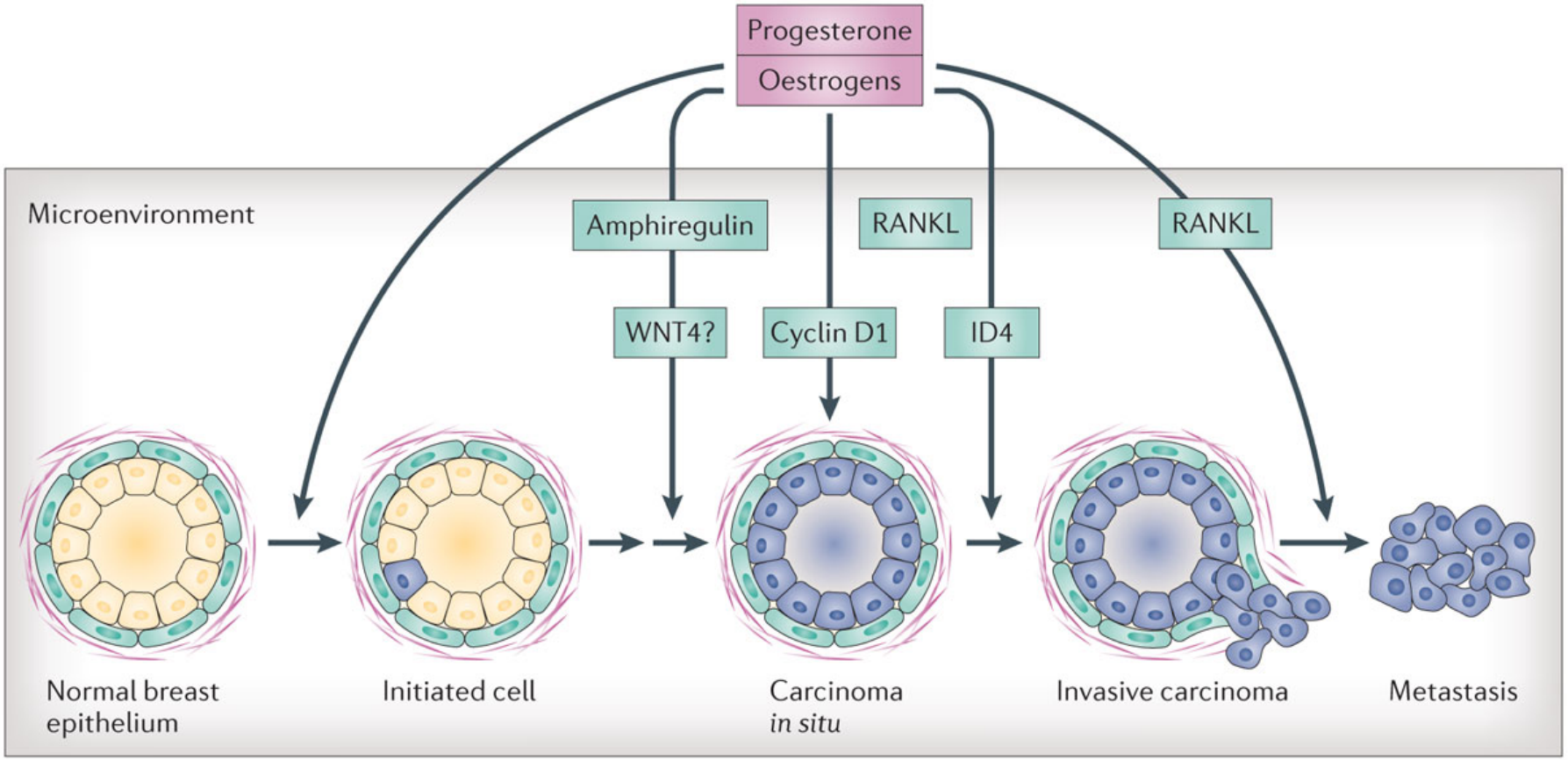
Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.
Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Robbins 8E

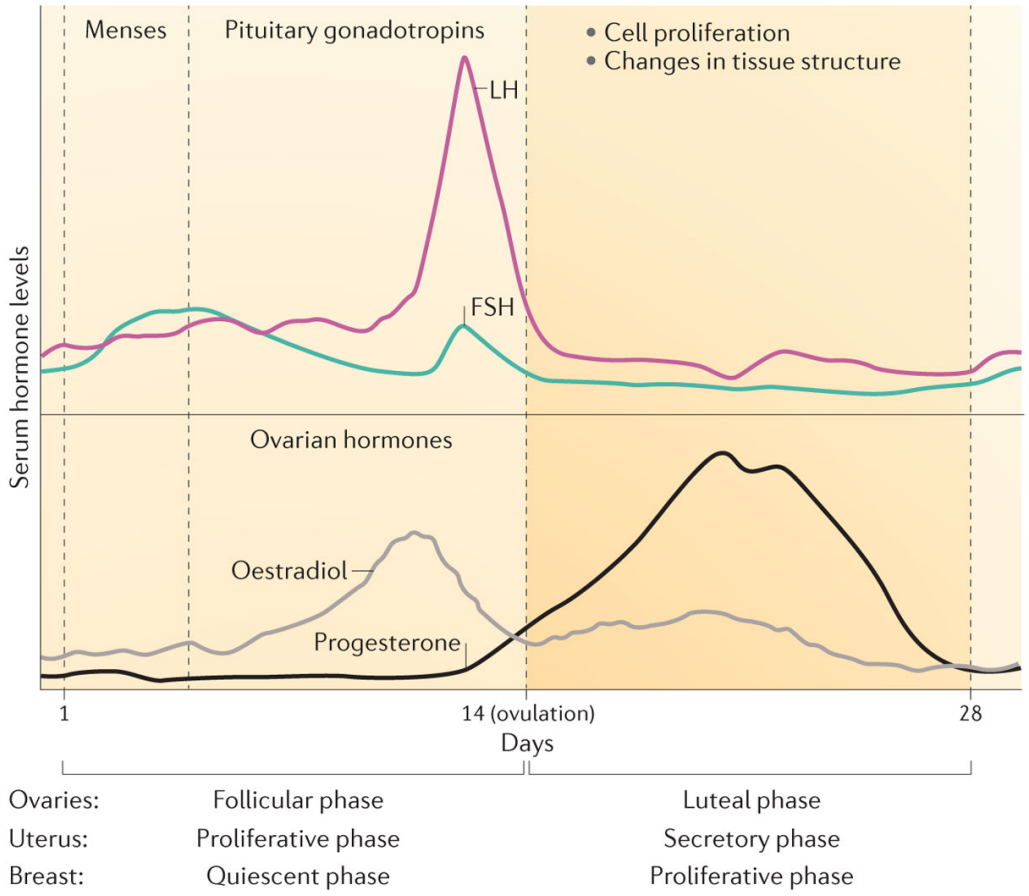
REVIEWS

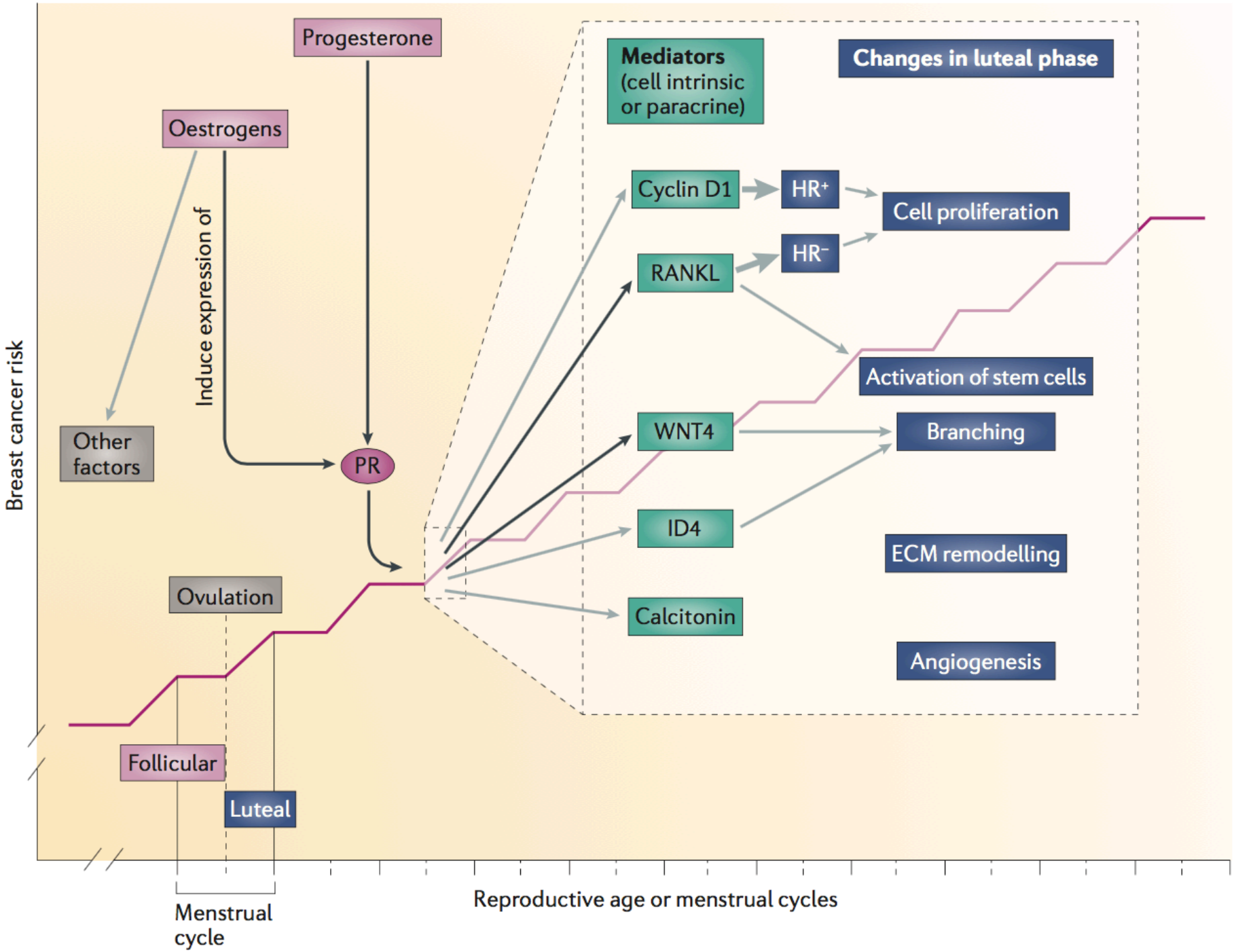
Progesterone signalling in breast cancer: a neglected hormone coming into the limelight



REVIEWS

Progesterone signalling in breast cancer: a neglected hormone coming into the limelight




Progesterone
Oestrogens
Induce expression of
Other factors
PR
Mediators (cell intrinsic or paracrine)
Changes in luteal phase
Cyclin D1
HR+
Cell proliferation
RANKL
HR−
Activation of stem cells
WNT4
Branching
ID4
ECM remodelling
Calcitonin
Angiogenesis
Ovulation
Follicular
Luteal
Menstrual cycle
Reproductive age or menstrual cycles
Breast cancer risk

At a glance

- Mutations are not always sufficient to drive breast carcinogenesis but additional factors determine whether genetically altered cells progress to the state during which they provoke clinically manifest disease.
- The ovarian steroid hormones, 17β-oestradiol and progesterone, are pivotal in the control of breast development and physiology and are intimately linked to mammary carcinogenesis. Their respective roles *in vivo* have begun to be dissected in the mouse model.
- 17β-oestradiol and progesterone act on a subset of cells that express the respective receptors and elicit paracrine signalling.
- Progesterone has emerged as the major mitogen in the adult mammary epithelium in both mice and humans.
- The major proliferative control axis progesterone–receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) is conserved between mice and humans.
- Interfering with progesterone receptor (PR) signalling and paracrine signalling holds promise for breast cancer prevention and therapy.

Breast cancer – risk factors

Risk factor	RR
• Delayed menopause (1 year)	1.14
• BMI (>29,7 Kg/m2)	1.48
• Alcohol consumption (20g /day x 5 years)	1.28
• HT for 5 years (WHI)	1.26
• HT + 20g alcohol / day (5 years)	1.99
• Age at 1st delivery > 30 years	1.48

Shah NR, Exp Opin Pharmacotherapy 2006

Table 1. Risk Factors for Breast Cancer in Women

- Advanced age
- First-degree relative with breast cancer
- Genetic predisposition: BRCA1 or BRCA2 gene
- Early menarche
- Late menopause
- Nulliparity
- First full-term pregnancy after age 30
- Personal history of breast, ovarian, or endometrial cancer
- Obesity/increased BMI
- High breast-tissue density
- Long-term or high-dose estrogen replacement therapy
- Prior radiation to breast area, as in treatment for Hodgkin's disease

BMI = body mass index.
Source: National Institutes of Health.

Table 3. Factors That Increase the Relative Risk for Breast Cancer in Women

Relative Risk	Factor
>4.0	• Female
	• Age (65+ versus <65 years, although risk increases across all ages until age 80)
	• Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2)
	• Two or more first-degree relatives with breast cancer diagnosed at an early age
	• Personal history of breast cancer
	• High breast tissue density
	• Biopsy-confirmed atypical hyperplasia
2.1-4.0	• One first-degree relative with breast cancer
	• High-dose radiation to chest
	• High bone density (postmenopausal)
1.1-2.0	
Factors that affect circulating hormones	• Late age at first full-term pregnancy (>30 years)
	• Early menarche (<12 years)
	• Late menopause (>55 years)
	• No full-term pregnancies
	• Never breastfed a child
	• Recent oral contraceptive use
	• Recent and long-term use of hormone replacement therapy
	• Obesity (postmenopausal)
Other factors	• Personal history of endometrium, ovary, or colon cancer
	• Alcohol consumption
	• Height (tall)
	• High socioeconomic status
	• Jewish heritage

Adapted with permission from Hulka et al, 2001.

Breast Cancer
Case- control studies

Author	Cases	Controls	Comparison	OR (95% CI)
Braga et al. 1996	2,569 (3.3)	2,588 (2.9)	Fertility treatment vs. none	1.1 (0.8–1.5)
			FD use vs. no use	1.4 (0.7-1.8)
Weiss et al. 1998	2,173 (8.5)	1,990 (7.4)	CC or other drug use among those with difficulty conceiving	0.8 (0.9–1.0
			Medications among women with difficulty maintaining a pregnancy	1.0(0.6-1.3)

Breast Cancer
Case- control studies

Author	Cases	Controls	Comparison	OR (95% CI)
Ricci et al. 1999	3,415	2,916	Ever FD vs. no use Nulliparous women Parous women	1.2 (0.5–2.6) 0.6 (0.2–2.3) 2.2 (0.7–6.6)
Burkman et al. 2003	4,566	4,676	Ever FDs vs. no use ≥6 cycles CC ≥6 cycles hMG Ever FDs vs. no use in infertile women ≥6 cycles CC ≥6 cycles HMG	0.9 (0.8–1.2) 1.0 (0.7–1.3) 2.7 (1.0–6.9) 1.2 (0.8–1.7) 1.2 (0.7–2.0) 3.8 (1.2–11.8)

Breast Cancer
Cohort trials

Author	Cohort	SIR(95% CIs):		RR (95% CI)	
Rossing et al. 1996	3,837			CC	0.5 (0.2–1.2)
				≥12 cycles	0.6 (0.2–2.4)
				hCG	0.5 (0.2–1.8)
Modan at al. 1998	2,496	No Tx	1.4 (1.0–2.0)		
		All Tx	1.1 (0.7–1.6)		
		CC	1.2 (0.7–1.9)		
		CC + hMG	1.6 (0.7–3.4)		
Venn et al. 1999	29,666	No IVF	0.9 (0.7–1.2)		
		IVF	0.9 (0.7–1.1)		

Breast Cancer
Cohort trials

	Cohort	SIR(95% CIs):		RR (95% CI)	
Klip et al. 2002	23,592	No IVF	1.0 (0.7–1.4)	IVF	1.0 (0.6–1.5)
		IVF	1.1 (0.8–1.4)		
		≥7 cycles	0.8 (0.2–2.1)		
Doyle et al. 2002	5,556	No Tx	1.2 (0.6–2.0)	Tx	1.0 (0.5–1.9)
		Tx	1.2 (0.8–1.6)		
Brinton et al. 2004	12,193	No CC	1.3 (1.1–1.5)	CC	1.0 (0.8–1.3)
		CC	1.3 (1.1–1.6)	≥20 y F/ U	1.4 (0.9–2.1)
		No hMG	1.3 (1.1–1.4)	hMG	1.1 (0.7–1.6)
		hMG	1.4 (0.9–2.0)	≥20 y F/ U	1.5 (0.8–3.2)

Breast Cancer

- E3N study (98,000 women)
- 6,602 reported fertility problems
- 2571 invasive breast cancers in 10 years follow up.

	n	Woman years	Cases	RR(95%CI)
Treated for infertility				
Never	85953	831.342	2388	
Ever	6602	63.668	183	0.95(0.82-1.11)
Treated with fertility drugs				
Never	85953	831.342	2388	
Ever	4843	46.529	133	0.94 (0.78-1.12)

Hum Reprod 2004

Fertility drugs and the risk of breast cancer: a meta-analysis and review

Infertile women treated with fertility enhancing drugs vs. infertile untreated controls → risk of breast cancer?

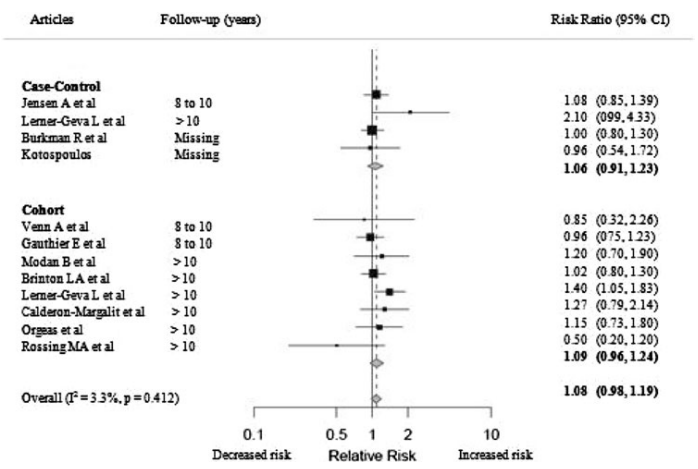
8 case-control studies

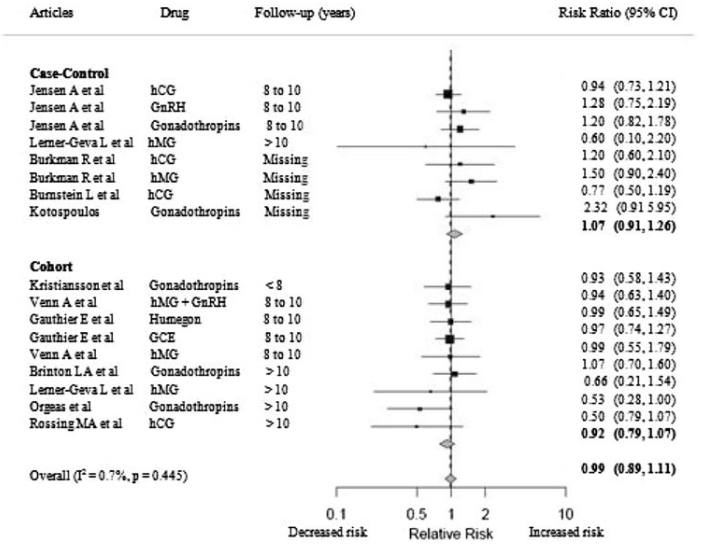
15 cohort studies

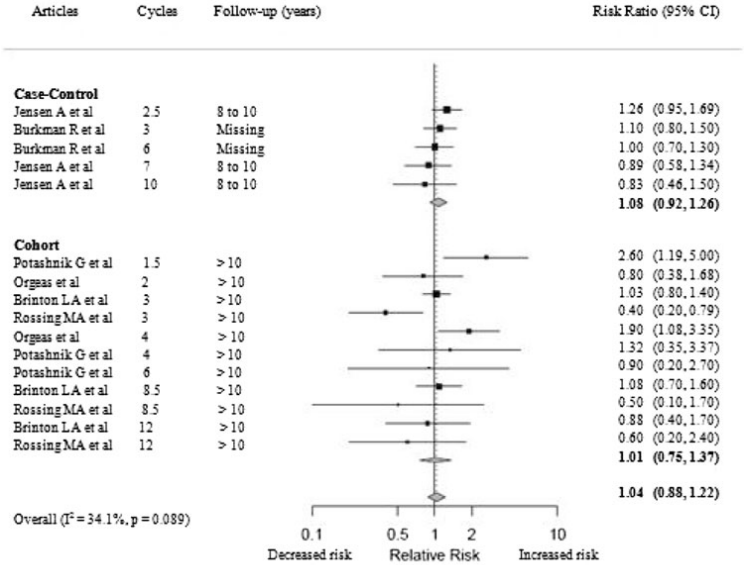
MEDLINE, Cochrane, Scopus
1948 – August 2009

Breast Cancer Res Treat (2010) 124:13–26

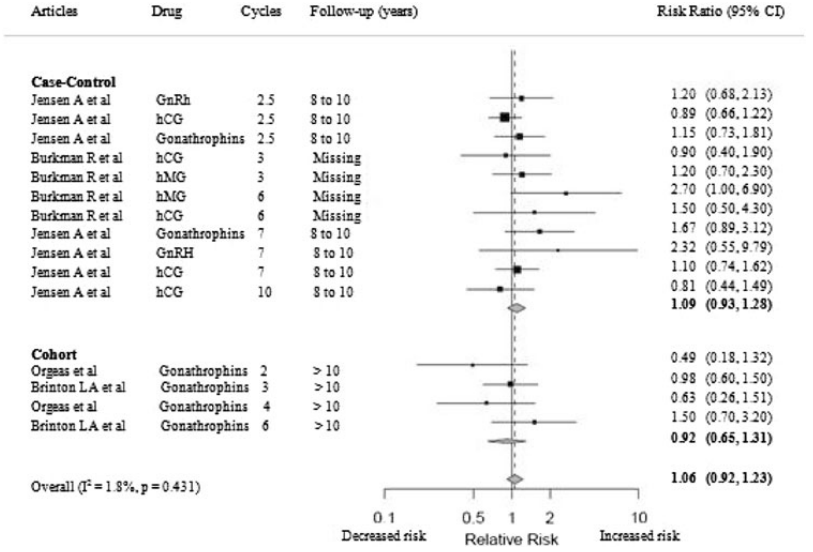
Fertility drugs and the risk of breast cancer: a meta-analysis and review







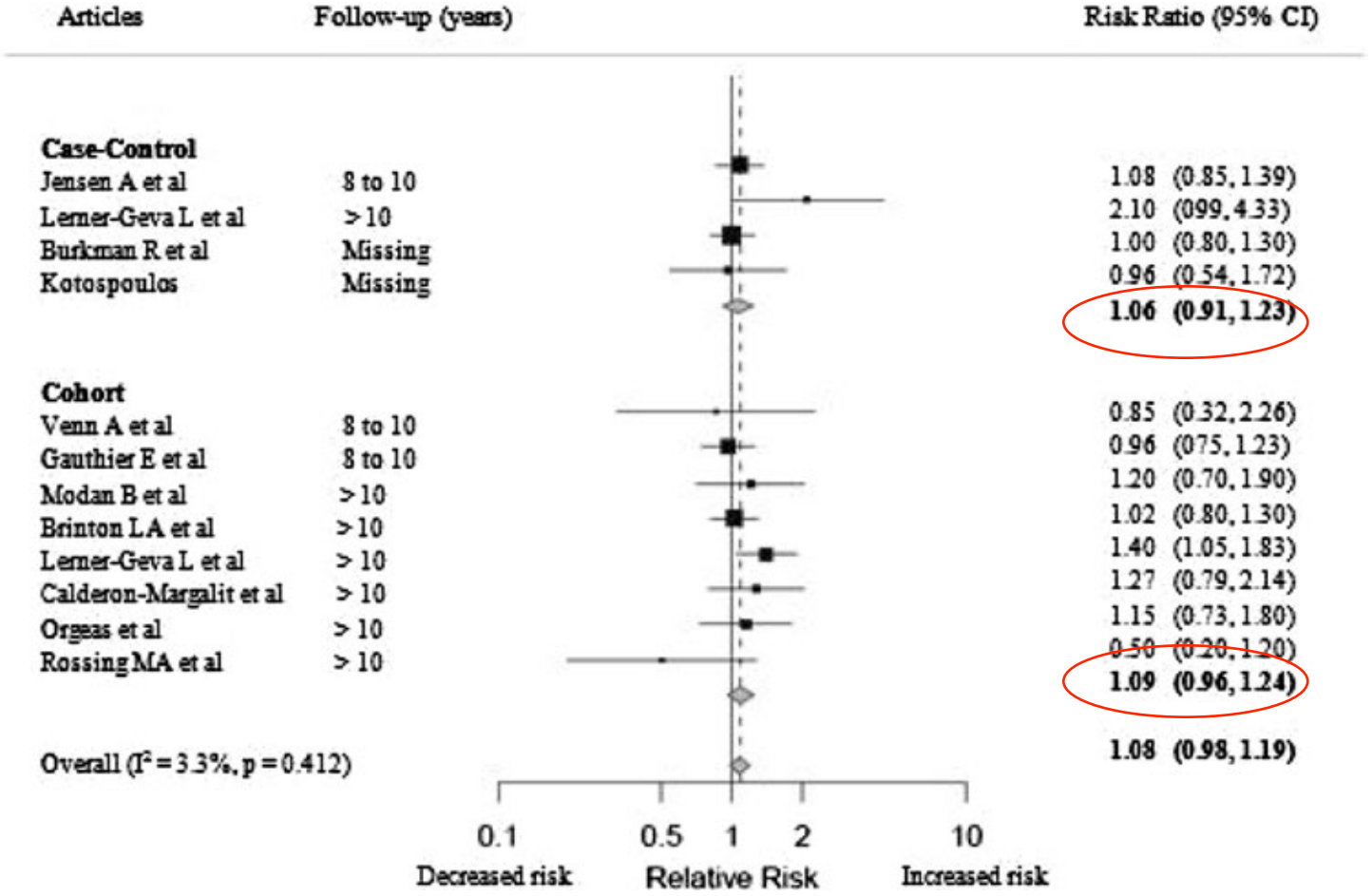
Note: Weights are from random effects model



Breast Cancer Res Treat (2010) 124:13–26

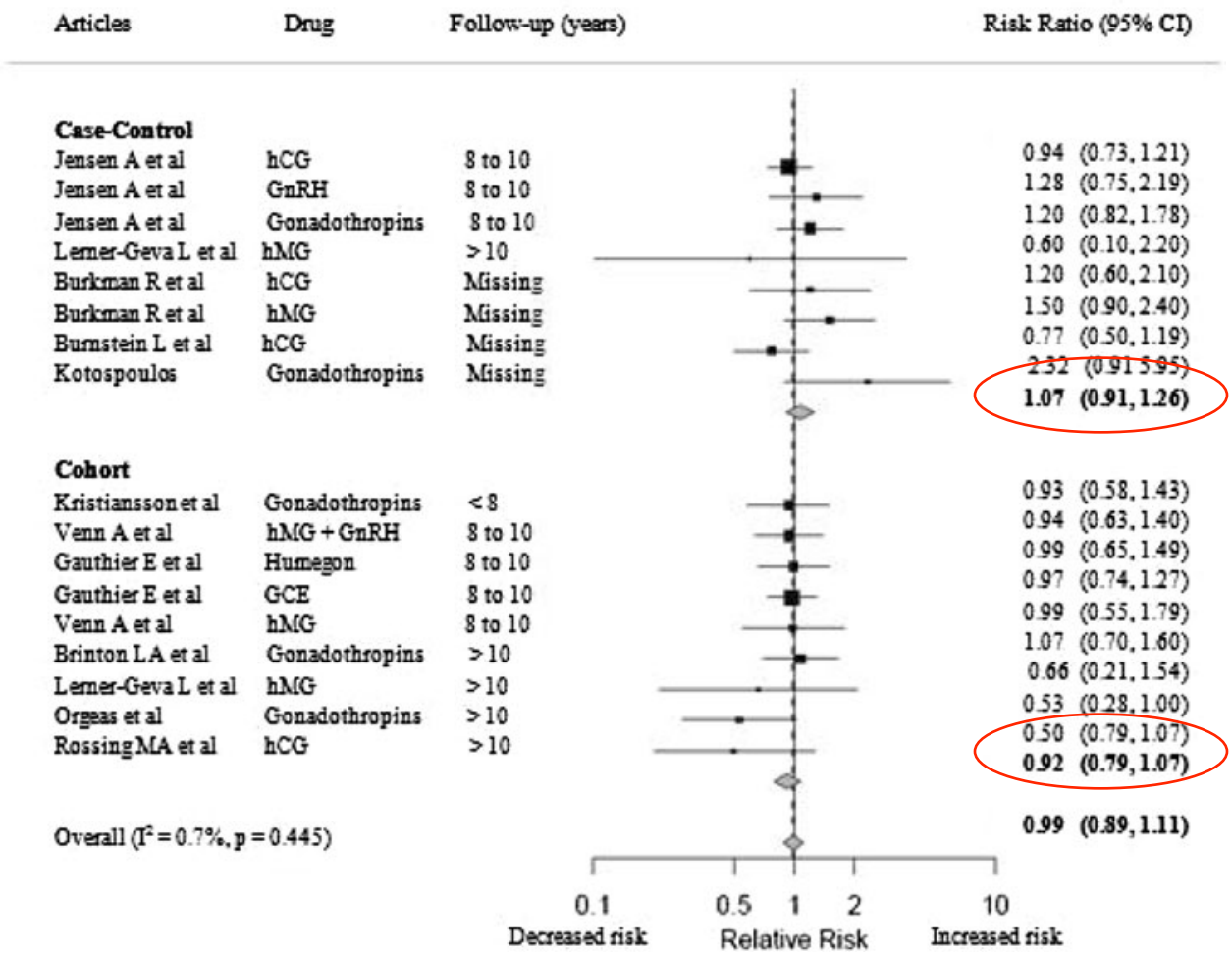
Breast Cancer
Meta-analysis

- Clomiphene and the risk of breast cancer



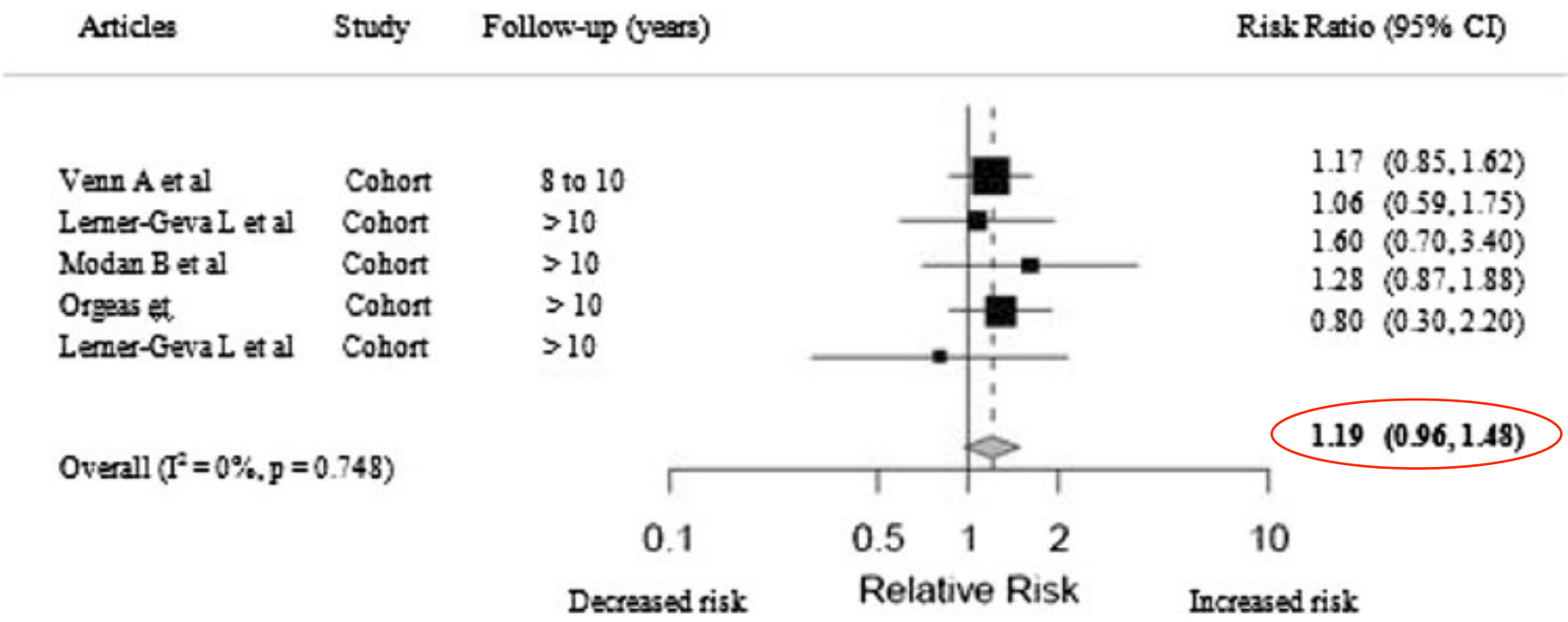
Breast Cancer
Meta-analysis

- Other specific fertility drugs and the risk of breast cancer



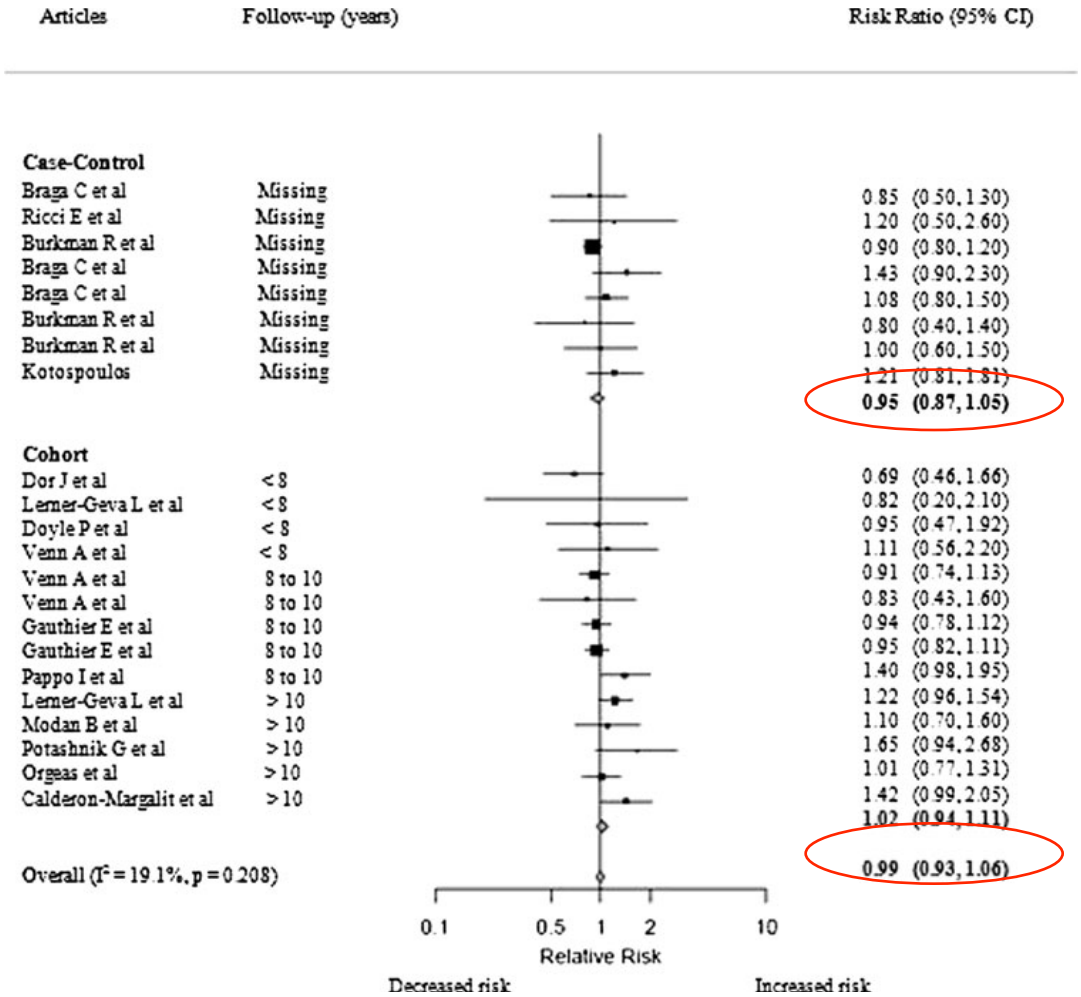
Breast Cancer
Meta-analysis

- Clomiphene followed by hMG and the risk of breast cancer



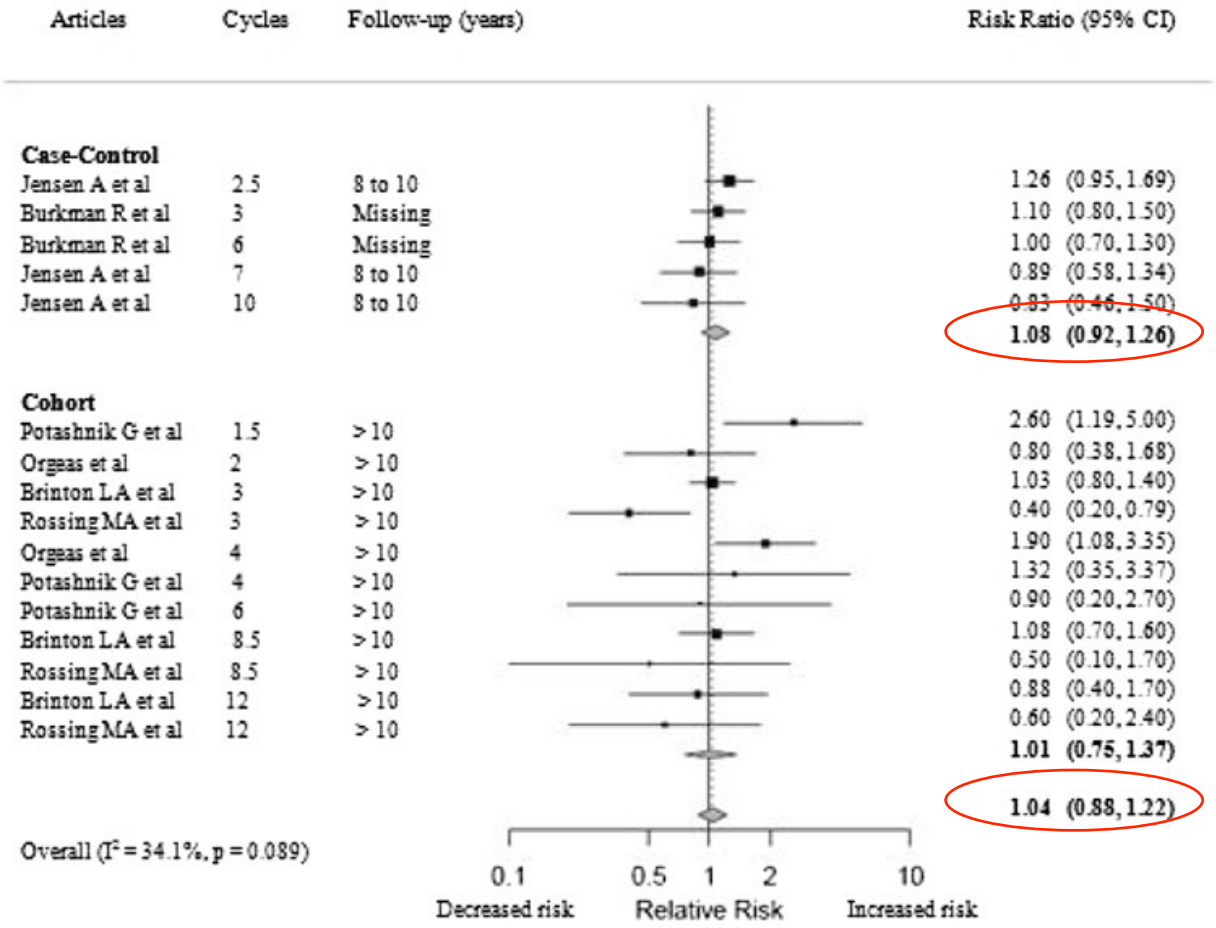
Breast Cancer
Meta-analysis

- Other fertility drugs and the risk of breast cancer



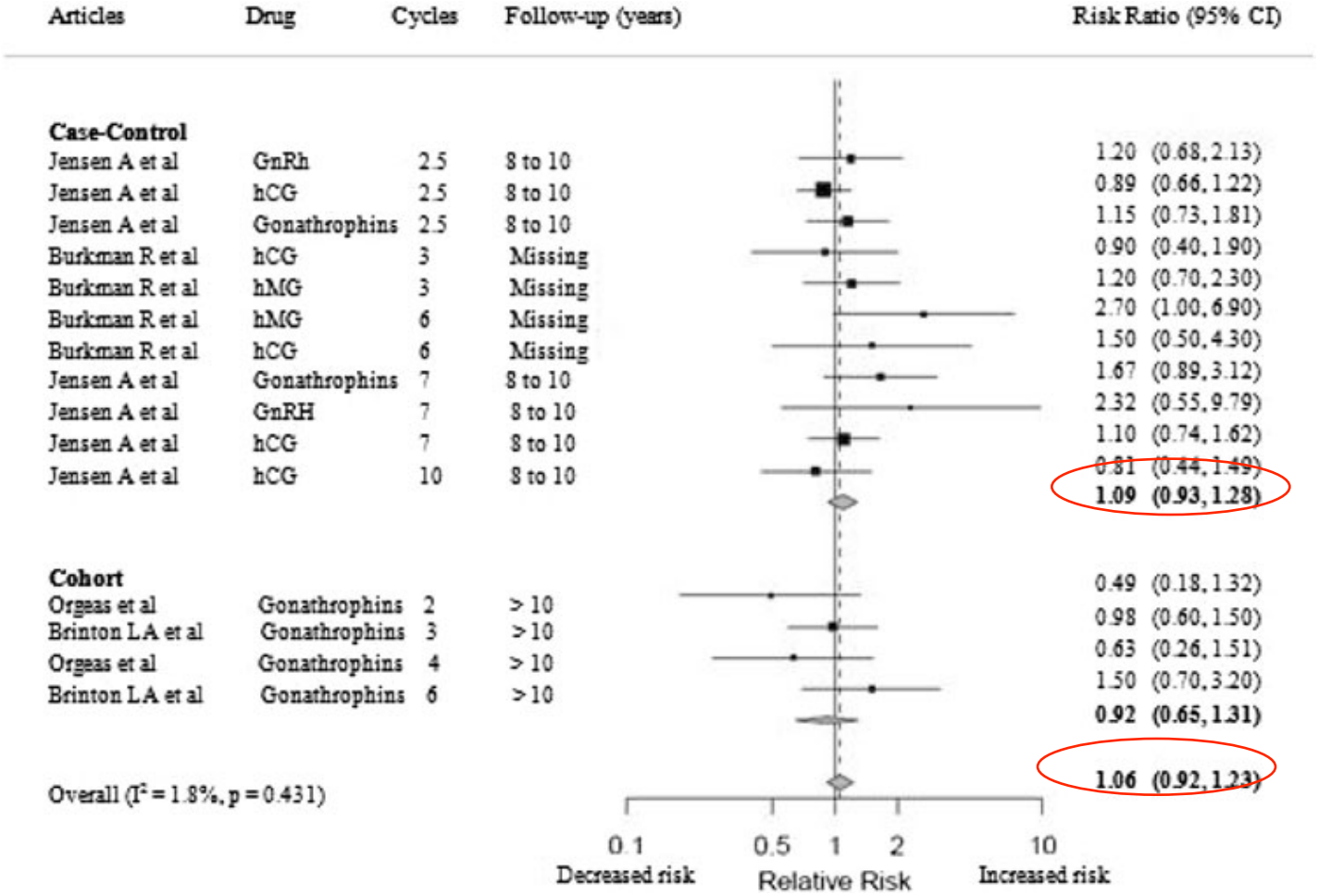
Breast Cancer
Meta-analysis

- Cycles of clomiphene and the risk of breast cancer.



Breast Cancer
Meta-analysis

- Cycles of other specific fertility drugs and the risk of breast cancer



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

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

Methods:
An extended follow-up was conducted among a cohort of 12,193 women evaluated for infertility between 1965–1988 at five U.S. sites.

Follow-up through 2010 was achieved for 9,892 women (81.1% of the eligible population) First evaluation for infertility was at 30.1 years.

During a median of 30.0 years of follow-up,749 breast cancers were identified among study participants, with a mean age at diagnosis of 52.7 years.

A total of 38.1% of the patients had been exposed to clomiphene and 9.6% to gonadotropins.

Cancer Epidemiol Biomarkers Prev. 2014 April ; 23(4): 584–593.

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

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Results

There was some evidence of increasing risk with increasing cycles of clomiphene, with the risk rising to 1.37 (0.97–1.92) for those who received ≥12 cycles.

Ever use of gonadotropins was not associated with breast cancer risk (1.14, 0.89–1.44).Further, there were no trends according to dosage, number of cycles, or age at first use.

The risk among nulligravid women at follow-up was associated with a significant risk for invasive breast cancers (1.98, 95% CI 1.04–3.60)

Cancer Epidemiol Biomarkers Prev. 2014 April ; 23(4): 584–593.

By **ROBERT PREIDT** / **HEALTHDAY** / *April 4, 2014, 4:39 AM*

Fertility drugs may not raise breast cancer risk: study

Original Investigation

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

Key Points

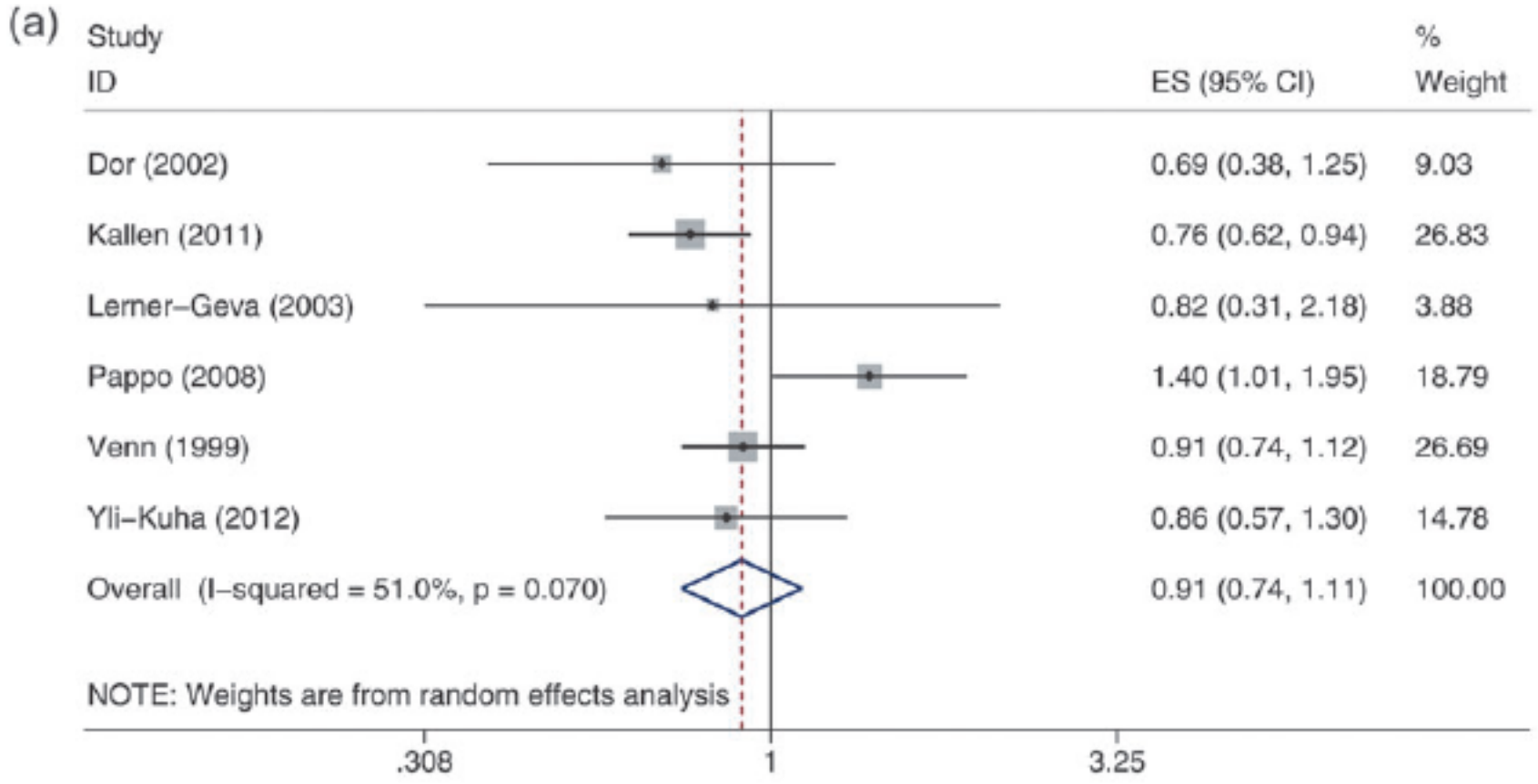
Question What is the long-term risk of breast cancer after ovarian stimulation for in vitro fertilization (IVF)?

Findings In this cohort study that included 25 108 women who underwent fertility treatments with a median follow-up of 21.1 years, breast cancer risk in IVF-treated women was not significantly different from that in the general population or in women who underwent other fertility treatments.

Meaning These findings are consistent with the absence of a significant increase in long-term risk of breast cancer among IVF-treated women.

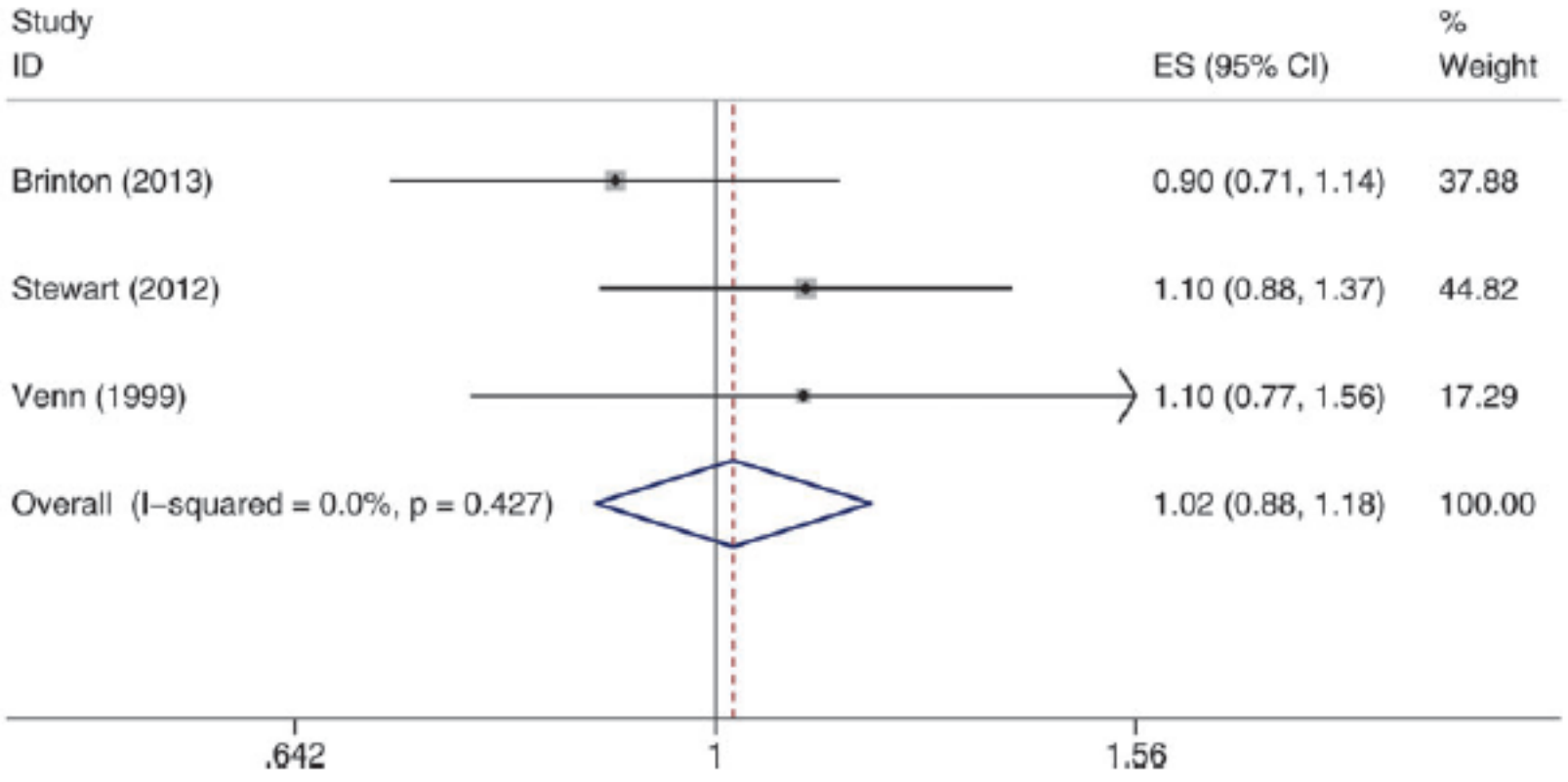
JAMA. 2016;316(3):300-312. doi:10.1001/jama.2016.9389

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



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

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

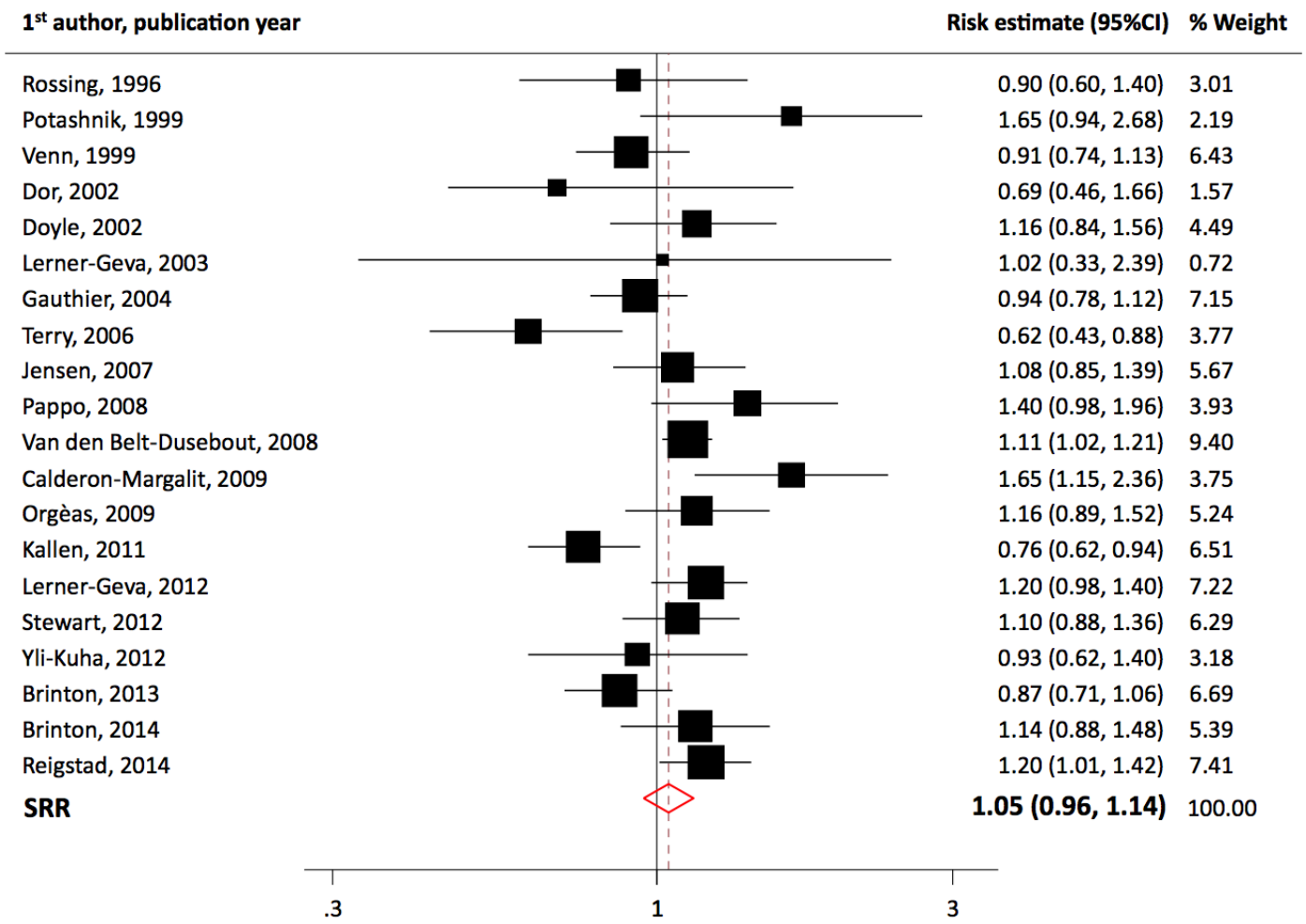


Human Reproduction Update, Vol.20, No.1 pp. 106–123, 2014

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



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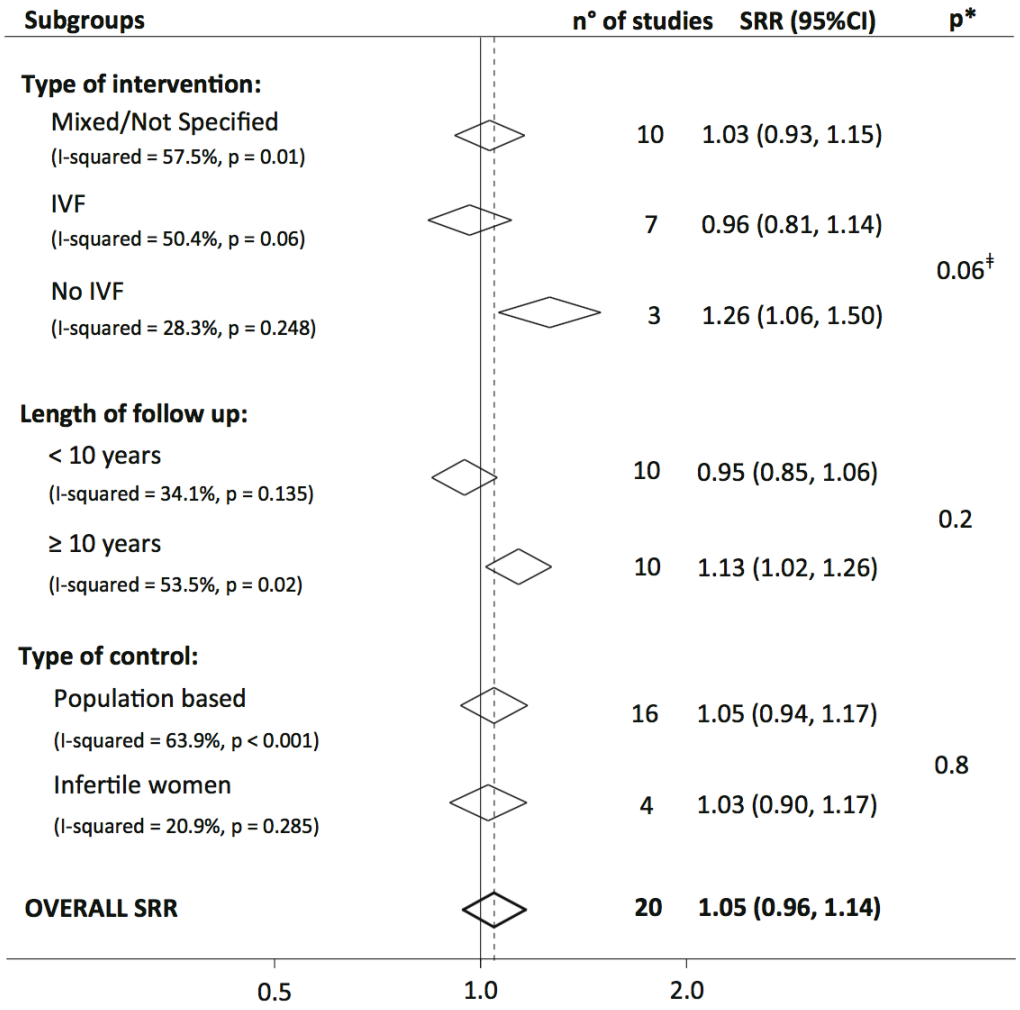

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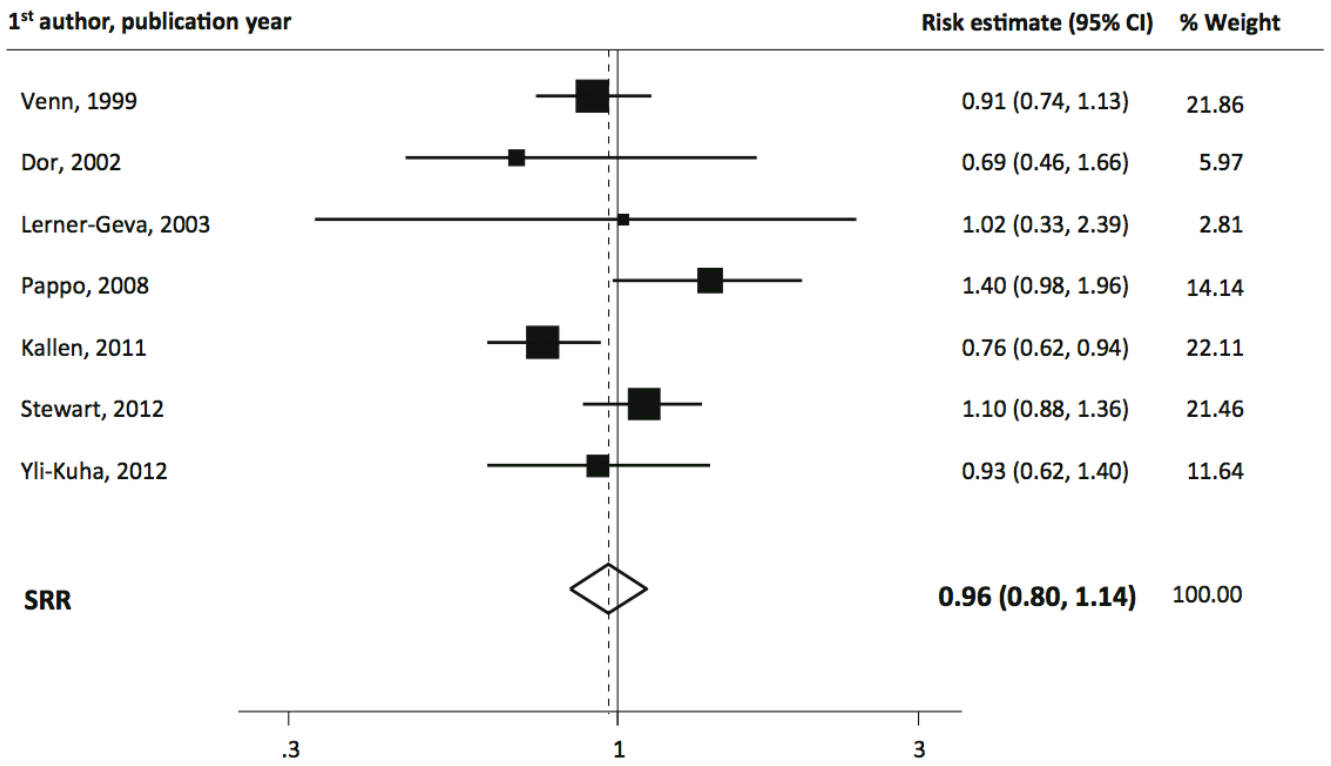

Fig. 4 In vitro fertilization (IVF) and breast cancer risk. *SRR* summary relative risks

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

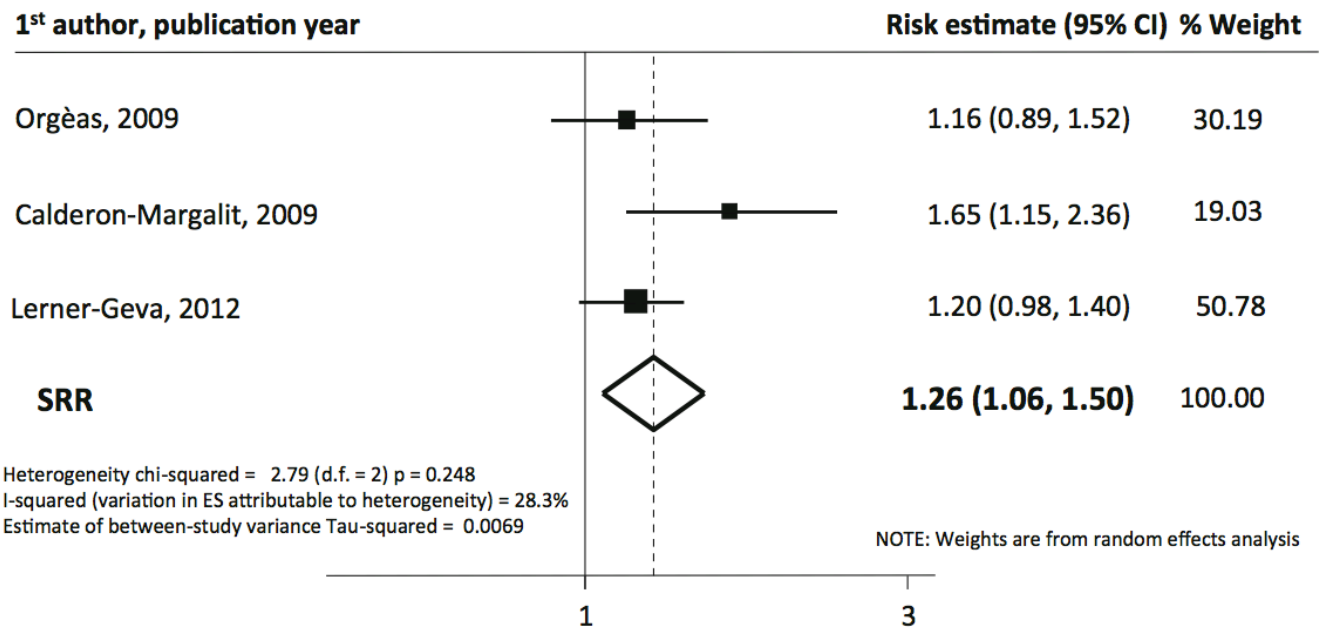

Fig. 5 Breast cancer risk in women treated without in vitro fertilization (IVF) procedures (enrollment < 1980). *SRR* summary relative risks

Endometrial Cancer

Endometrial Cancer

- Most studies show no association:
  - Less than 10 years F/U
  - Few cases (2-14)
- Infertility (1.8 times) and nulliparity (2.7 times) are associated with increased risk of endometrial cancer.
- No association with use of fertility drugs

Benshushan et al. Obstet. Gynecol. 2001

Endometrial Cancer

- Cohort study of 8,431 infertile women in U.S
  - 39 uterine/endometrial cancers
- Results:

• Nulligravid:	RR:	3.5 (1.3-9.3)
• Obese:	RR:	6.2 (1.2-30)
• Obese and nulligravid	RR:	12.5 (1.5-108)

  - No increased risk with the use of gonadotropins
  - Increased risk of uterine cancer with clomiphene citrate
    - >900 mg of CC RR:1.9 (0.9-4.0)
    - More than 6 cycles: RR:2.16 (0.9-5.2)

Althuis et al. Am. J. Epidem. 2005

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Review

Does fertility treatment increase the risk of uterine cancer? A meta-analysis

Study or Subgroup	Fertility Treatment Events	Fertility Treatment Total	Non-Fertility Treatment Events	Non-Fertility Treatment Total	Weight	Odds Ratio M-H, Random, 95% CI
Brinton	34	67608	7	19795	18.2%	1.42 [0.63, 3.21]
Doyle	3	4188	1	1231	6.8%	0.88 [0.09, 8.48]
Kristiansson	78	8716	14882	640059	23.7%	0.38 [0.30, 0.47]
Lerner-Geva	17	1281	13	1150	19.2%	1.18 [0.57, 2.43]
Modan	13	1309	8	1187	17.4%	1.48 [0.61, 3.58]
Venn	5	20656	7	9044	14.6%	0.31 [0.10, 0.99]
Total (95% CI)		**103758**		**672466**	**100.0%**	**0.78 [0.39, 1.57]**
Total events	150		14918			

Heterogeneity: $Tau^2 = 0.52$; $Chi^2 = 24.31$, $df = 5$ ($P = 0.0002$); $I^2 = 79\%$

Test for overall effect: $Z = 0.69$ ($P = 0.49$)

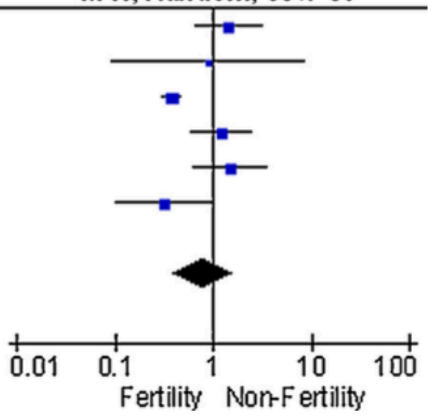

Fig. 2. Comparison of incidence of uterine cancer between 'fertility treatment' and 'non-fertility treatment' patient groups (random-effect model).

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Kristiansson	78	8716	14882	640059	96.3%	0.38 [0.30, 0.47]
Venn	5	20656	7	9044	3.7%	0.31 [0.10, 0.99]
Total (95% CI)		**29372**		**649103**	**100.0%**	**0.38 [0.30, 0.47]**
Total events	83		14889			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, $df = 1$ ($P = 0.74$); $I^2 = 0\%$

Test for overall effect: $Z = 8.72$ ($P < 0.00001$)

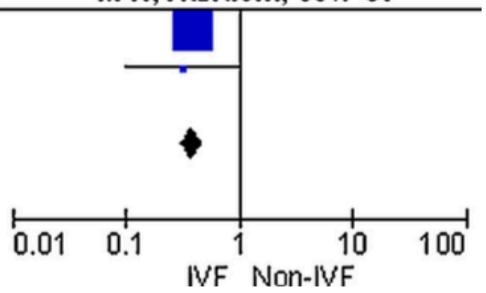
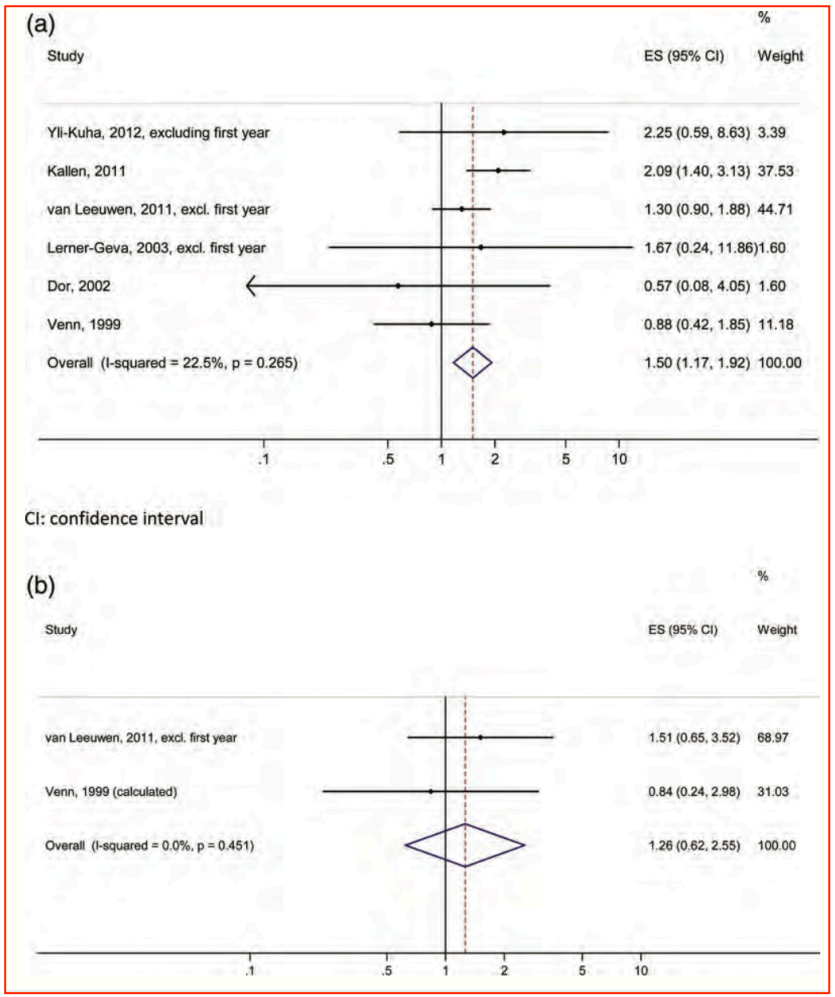


Fig. 3. Secondary outcome. Comparison of incidence of uterine cancer between 'IVF' and 'non-IVF treatment' patient groups (random-effect model).

Human Reproduction Update, Vol.19, No.2 pp. 105–123, 2013
Advanced Access publication on December 18, 2012 doi:10.1093/humupd/dms051

human reproduction update

Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis



Fertility drugs and Cervical cancer

- Scarce data exist regarding the association between fertility treatments and future risk of cervical cancer.
- In these studies, patients with a history of fertility treatments were found to have either a significantly lower risk of development of cervical cancer or with no increased risk of cervical cancer

Human Reproduction Update, Vol.19, No.2 pp. 105–123, 2013
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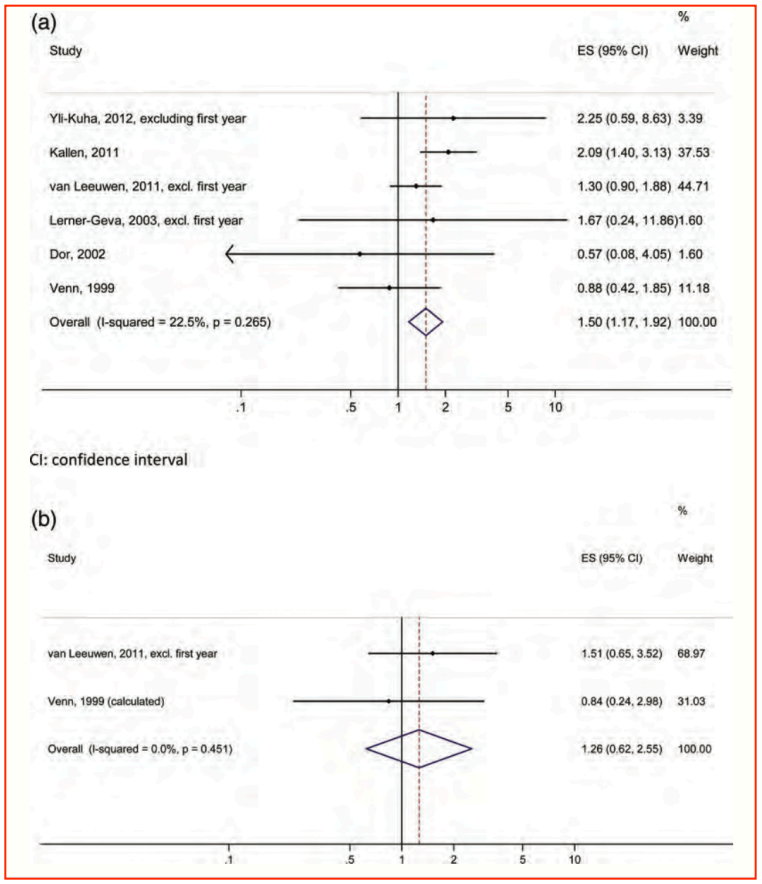
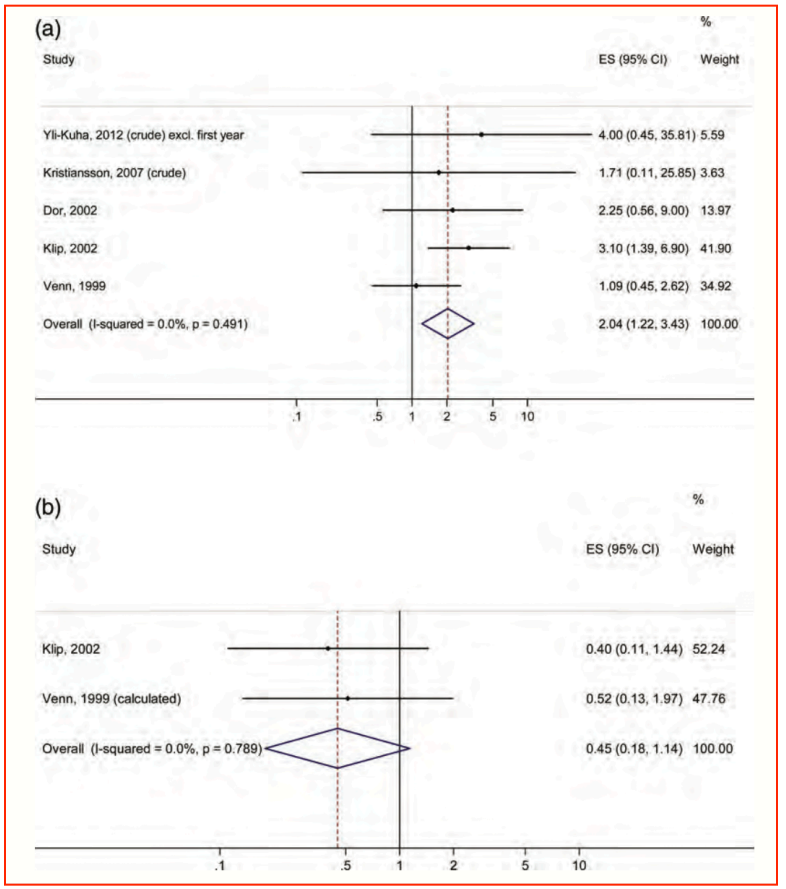
human reproduction update

Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis



Ovarian cancer



Endometrial cancer

ASRM PAGES

Fertility drugs and cancer: a guideline

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

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 low incidence of most of these cancers, and that the age of diagnosis of cancer typically is many years after fertility drug use. Based on available data, there does not appear to be a meaningful increased risk of invasive ovarian cancer, breast cancer, or endometrial cancer following the use of fertility drugs. Several studies have shown a small increased risk of borderline ovarian tumors; however, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors, and any absolute risk is small. Given the available literature, patients should be counseled that infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer; however, use of fertility drugs does not appear to increase this risk. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Fertility drugs and Other malignancies

- Design:
  - Retrospective cohort of 8422 women (155,527 women-years)
- Objective:
  - To evaluate the risk of developing Melanoma, thyroid, colon, and cervical cancer risks after clomiphene or gonadotropins.

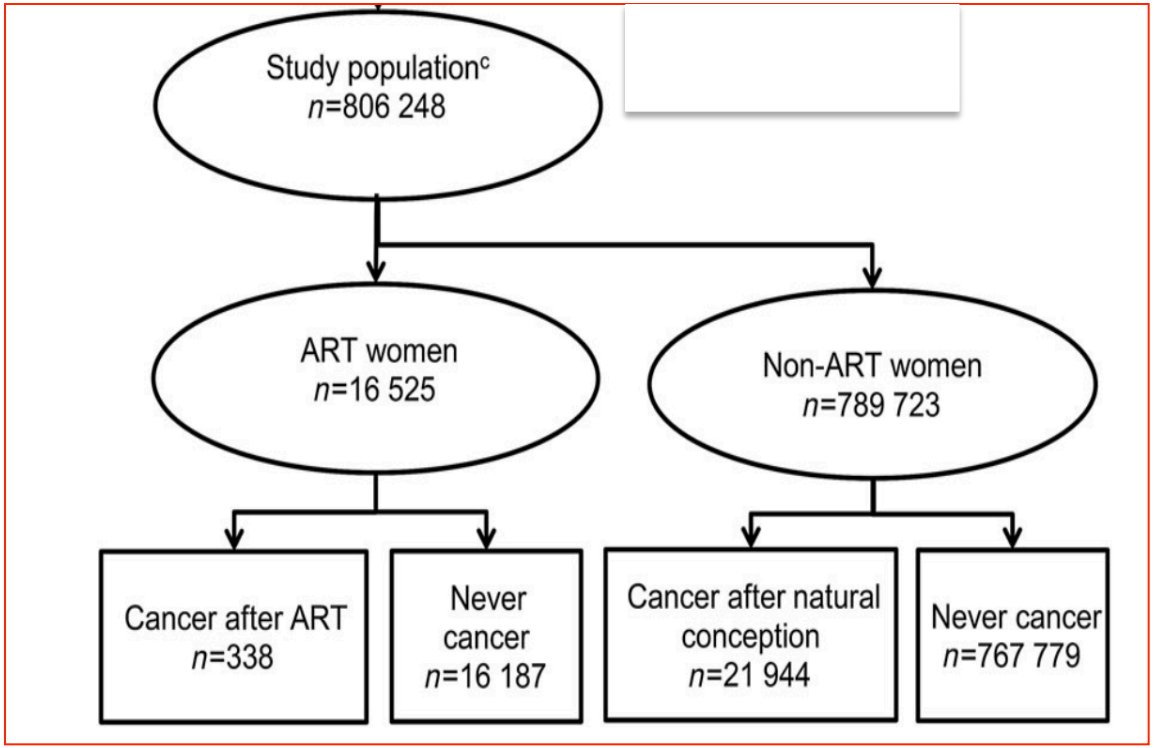
- Results:
  - ✓ Clomiphene use did not increase risk of melanoma, thyroid, cervical or colon cancer.
  - ✓ No relationship between clomiphene dose or cycles of use and cancer risk at any site.
  - ✓ Clomiphene use may impart stronger effects on risks of melanoma (RR=2.00; 95% CI, 0.9-4.6) and thyroid cancer among women who remained nulliparous (RR=4.23; 95% CI, 1.0-17.1).
  - ✓ Gonadotropins did not increase cancer risk for these sites.

Althuis et al. Am. J. Obstet.Gynecol. 2005

Cancer risk among parous women following assisted reproductive technology

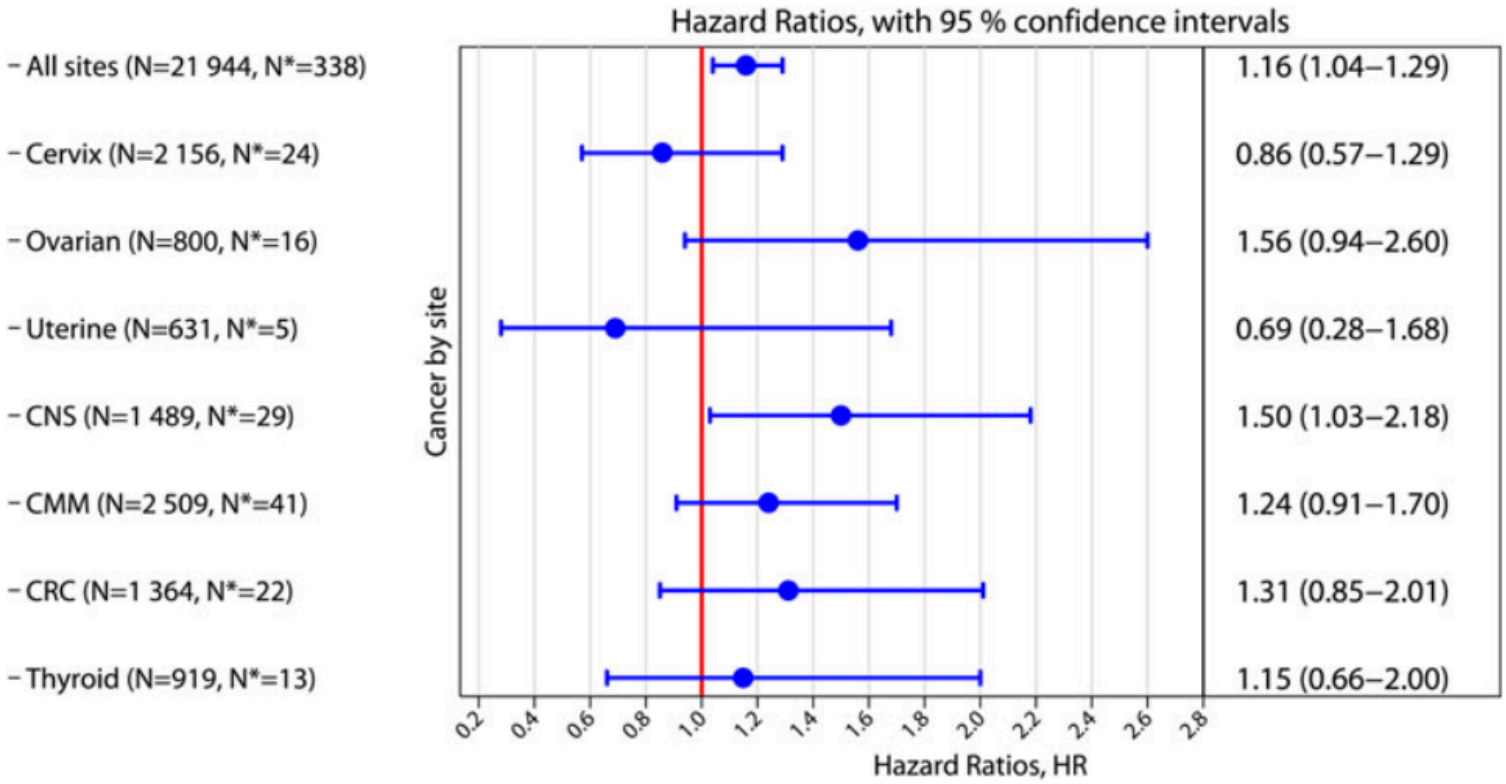
A population-based cohort consisting of all women registered in the Medical Birth Registry of Norway as having given birth between 1 January 1984 and 31 December 2010.

Median follow-up time for ART women was 7.3 years and for non-ART women 16.0 years



Human Reproduction, Vol.30, No.8 pp. 1952–1963, 2015

Cancer risk among parous women following assisted reproductive technology



Human Reproduction, Vol.30, No.8 pp. 1952–1963, 2015

Take home message.

- Infertility is an independent risk factor for malignancy
- Endometriosis is associated to ovarian cancer
- So far there is no strong evidence to associate use of fertility drugs and gynecologic cancer
- However the use of clomiphene citrate for more than three cycles should not be encouraged.
- A complete physical examination (including pap smear and breast exam) is necessary prior to any fertility treatment.

Thank you.

Pregnancy is a risky business

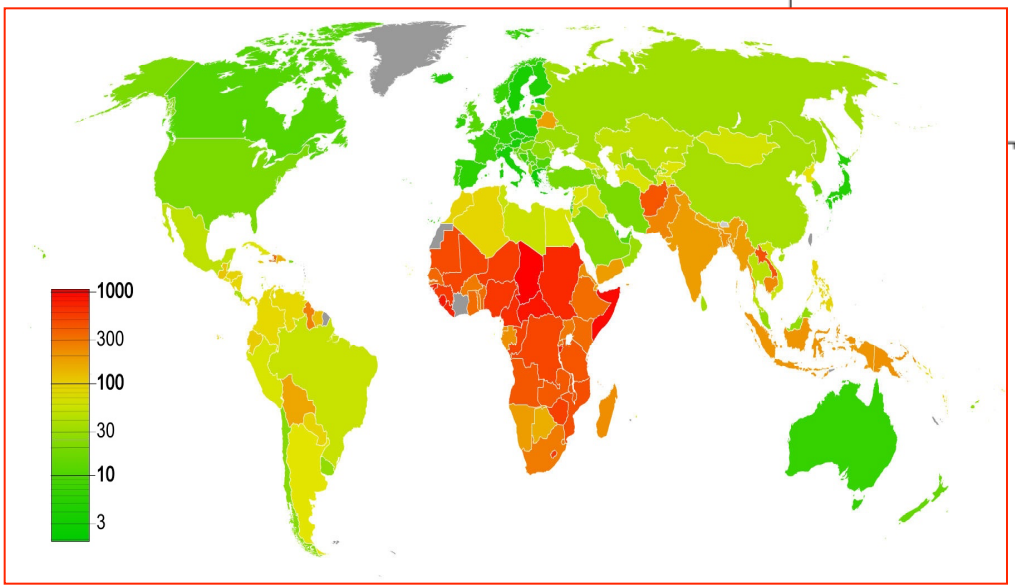
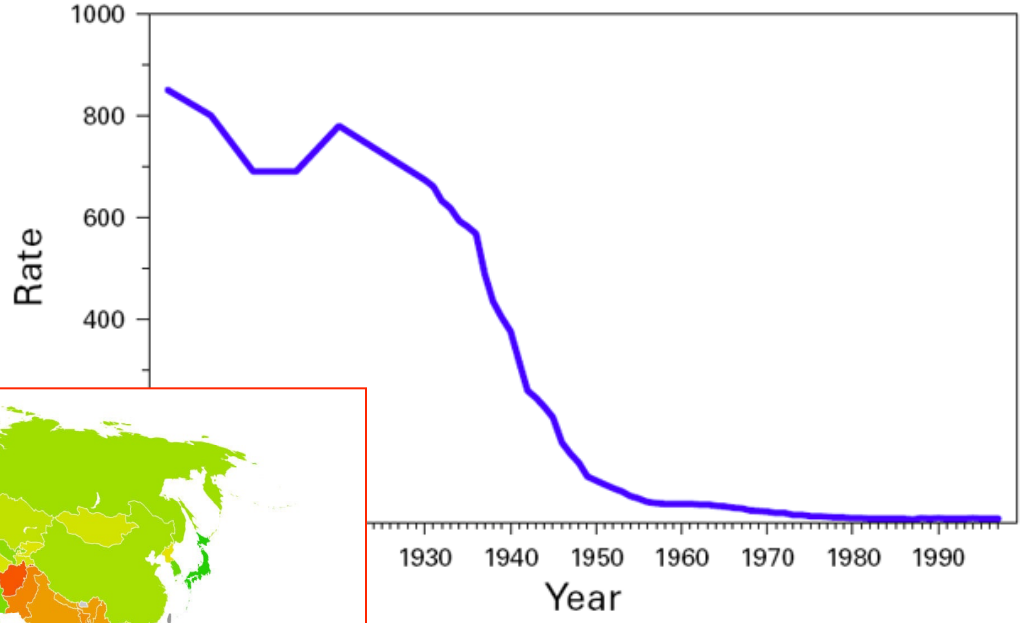


FIGURE 2. Maternal mortality rate,* by year — United States, 1900–1997



Human Reproduction Update, Vol.19, No.2 pp. 105–123, 2013
Advanced Access publication on December 18, 2012 doi:10.1093/humupd/dms051

human reproduction update

Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis

	Ovarian cancer				Endometrial cancer				Cervical cancer			
	n[a]	Effect estimate (95% CI)	*P*	Heterogeneity I^2, P^b	*n*[a]	Effect estimate (95% CI)	*P*	Heterogeneity I^2, P^b	*n*[a]	Effect estimate (95% CI)	*P*	Heterogeneity I^2, P^b
Approach preferring[c] estimates which excluded the first year of follow-up after IVF												
Analysis versus general population	6	**1.50 (1.17–1.92)**	0.001	22.5%, 0.265	5	**2.04 (1.22–3.43)**	0.007	0.0%, 0.491	5	0.86 (0.49–1.49)[R]	0.585	70.2%, 0.009
Subanalysis on SIRs	4	1.19 (0.86–1.64)	0.293	0.0%, 0.679	3	**1.97 (1.15–3.40)**	0.014	33.8%, 0.221	3	1.54 (0.47–5.09)[R]	0.480	64.0%, 0.062
Subanalysis on ORs	2	**2.10 (1.43–3.10)**	<0.001	0.0%, 0.918	2	2.86 (0.52–15.75)	0.227	0.0%, 0.632	2	**0.60 (0.52–0.70)**	<0.001	0.0%, 0.661
Analysis versus infertile women[d]	2	1.26 (0.62–2.55)	0.521	0.0%, 0.451	2	0.45 (0.18–1.14)	0.093	0.0%, 0.789	1	5.70 (0.28–117.20)	0.259	NC, NC[e]
Approach preferring[c] estimates derived from total follow-up												
Analysis versus general population	6	**1.65 (1.07–2.55)[R]**	0.022	52.1%, 0.064	5	**1.97 (1.18–3.27)**	0.009	0.0%, 0.553	5	0.85 (0.49–1.48)[R]	0.556	70.8%, 0.008
Subanalysis on SIRs	4	1.42 (0.74–2.76)[R]	0.294	58.1%, 0.067	3	**1.97 (1.15–3.40)**	0.014	33.8%, 0.221	3	1.54 (0.47–5.08)[R]	0.480	63.9%, 0.063
Subanalysis on ORs	2	**2.13 (1.45–3.13)**	<0.001	0.0%, 0.769	2	1.91 (0.46–8.04)	0.376	0.0%, 0.923	2	**0.60 (0.52–0.70)**	<0.001	0.0%, 0.518
Analysis versus infertile women[d]	2	1.05 (0.55–2.01)	0.874	0.0%, 0.685	2	0.45 (0.18–1.14)	0.093	0.0%, 0.789	1	5.70 (0.28–117.20)	0.259	NC, NC[e]

Infertility and Cancer

J Cancer Res Clin Oncol
DOI 10.1007/s00432-015-2035-x

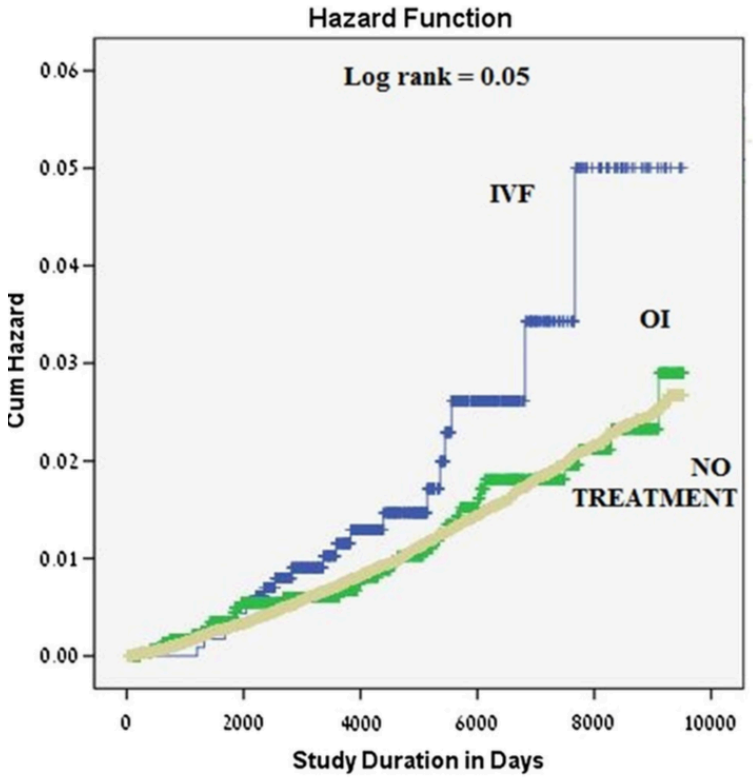
ORIGINAL ARTICLE - CLINICAL ONCOLOGY

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

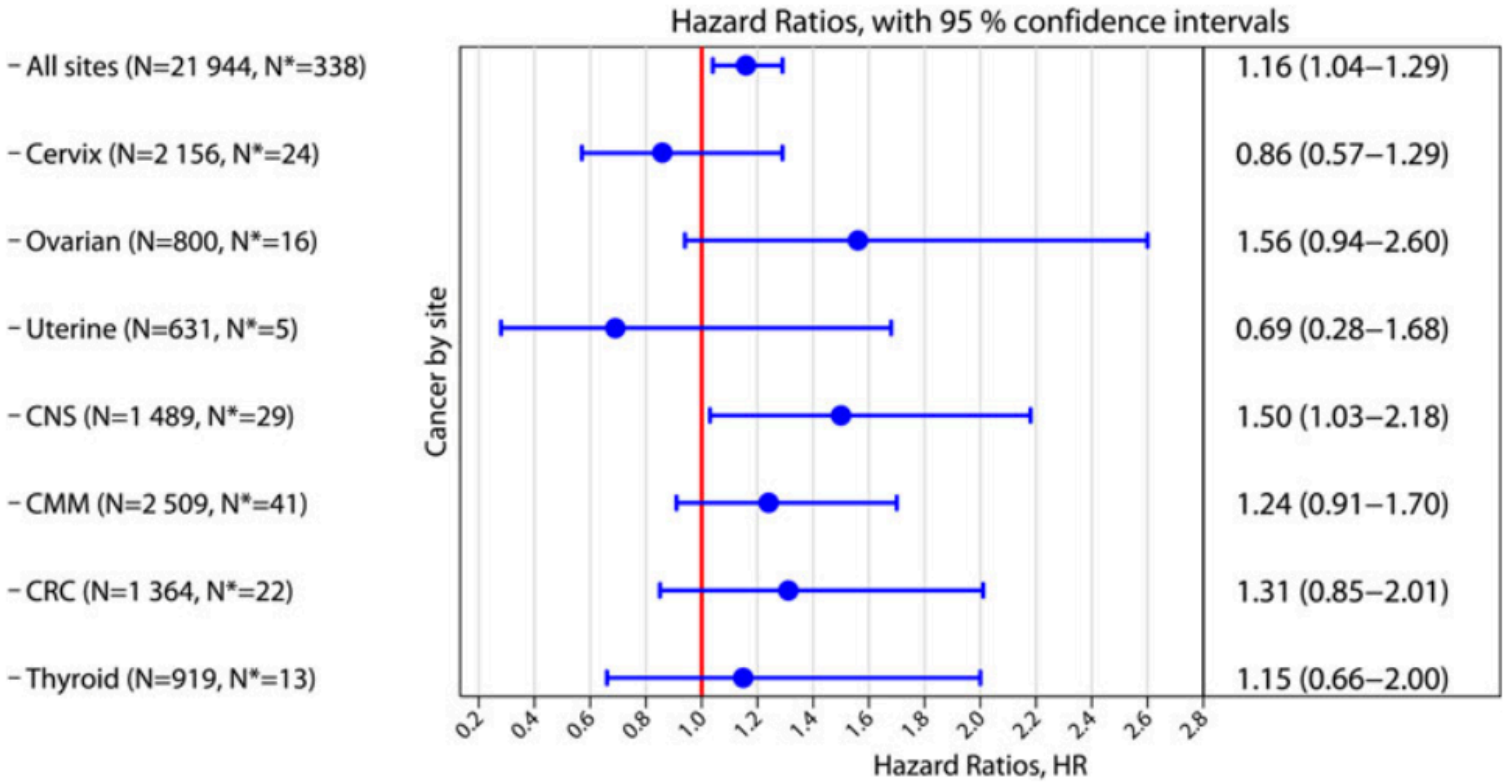
R. Kessous[1] · E. Davidson[3] · M. Meirovitz[1] · R. Sergienko[2] · E. Sheiner[1]

Table 2 Incidence of malignancies during the follow-up period in patients with and without a history of fertility treatment

	IVF ($n = 1149$) (%)	OI ($n = 3214$) (%)	No treatment ($n = 101{,}668$) (%)	p value
Ovary ($n = 58$)	0.26	0.03	0.05	0.009
Uterine ($n = 61$)	0.30	0.12	0.05	0.004
Cervix ($n = 239$)	0.3	0.2	0.2	0.868
Breast ($n = 528$)	0.4	0.5	0.5	0.926
Total	1.7	1.0	1.0	0.057

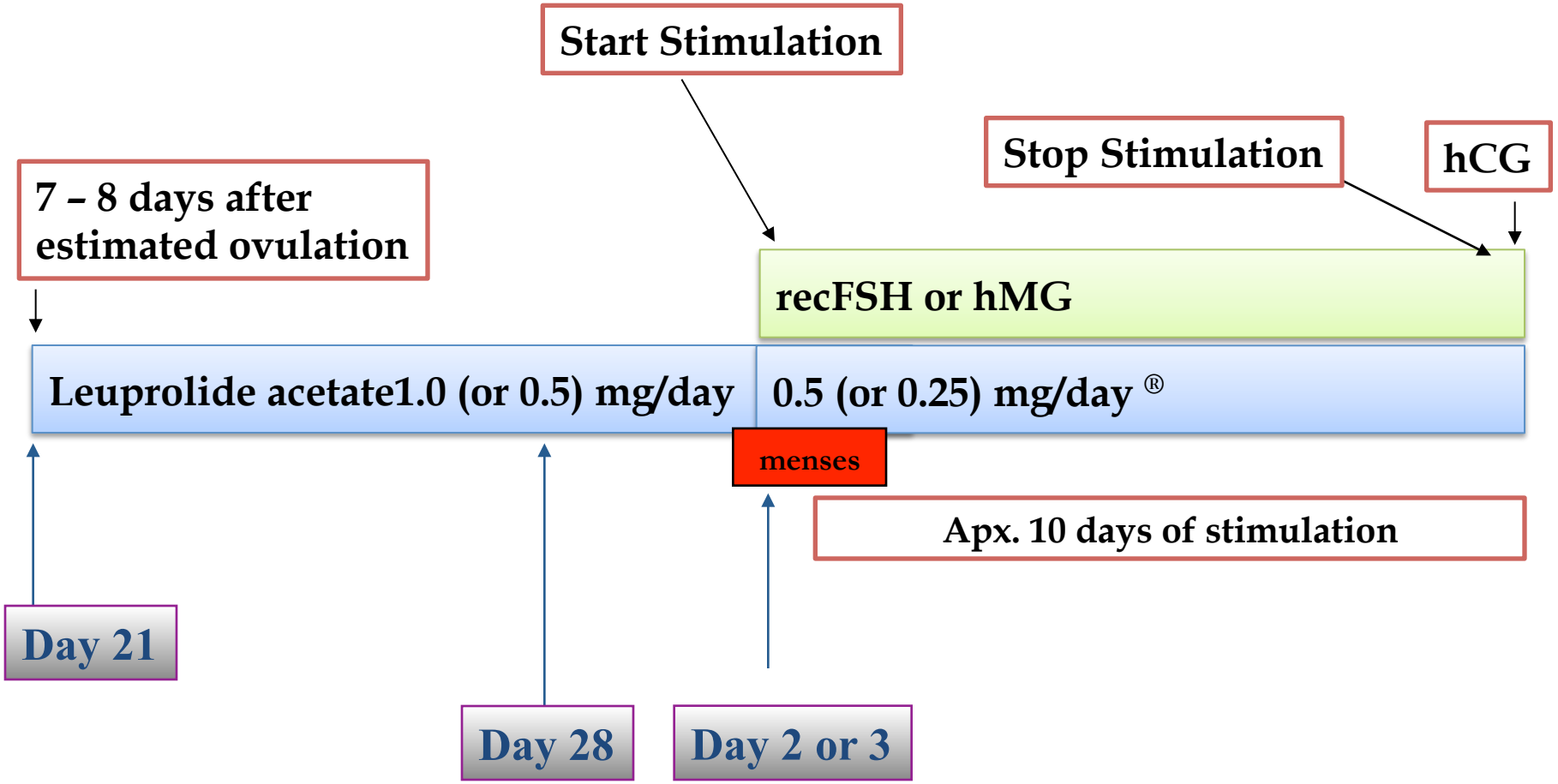


Cancer risk among parous women following assisted reproductive technology

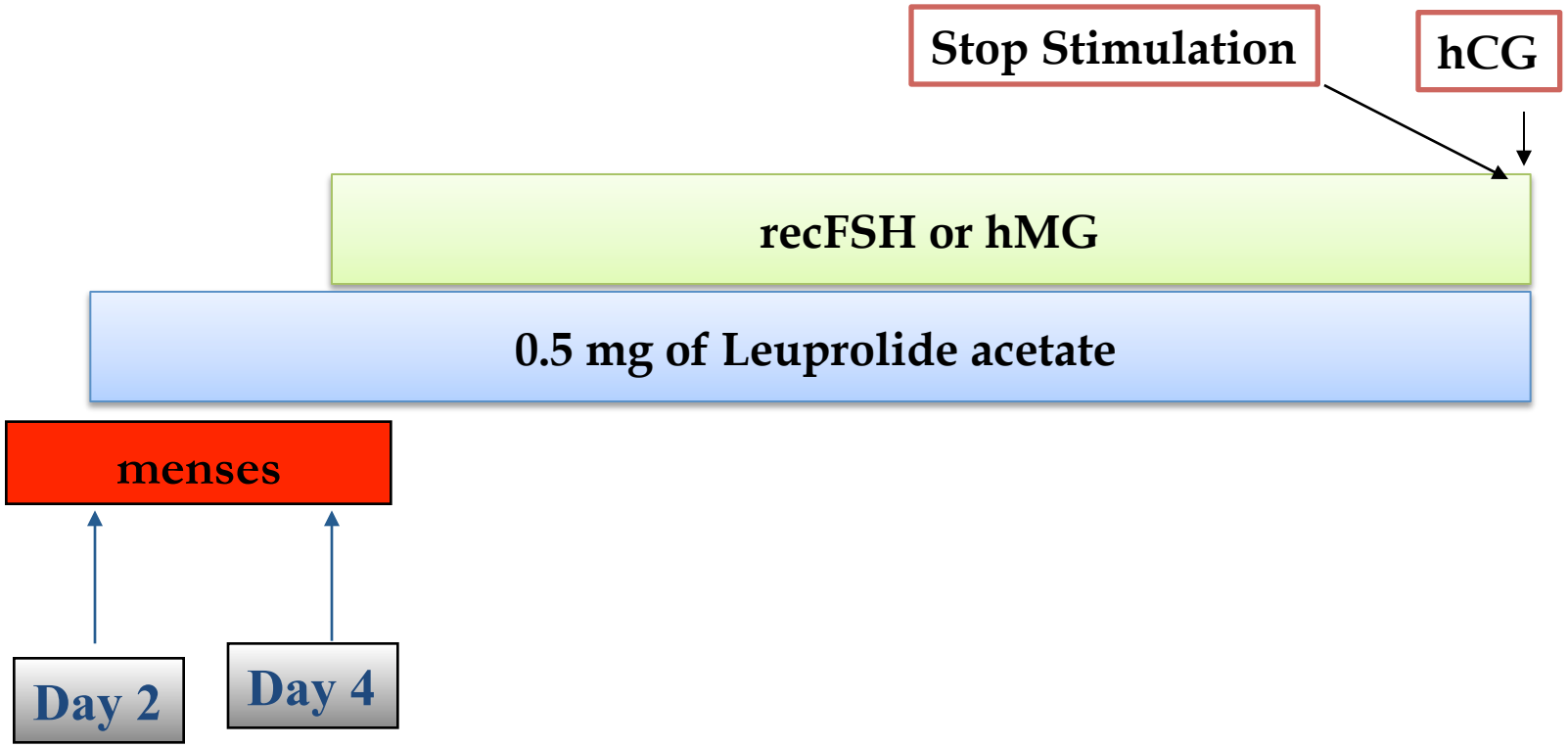


Human Reproduction, Vol.30, No.8 pp. 1952–1963, 2015

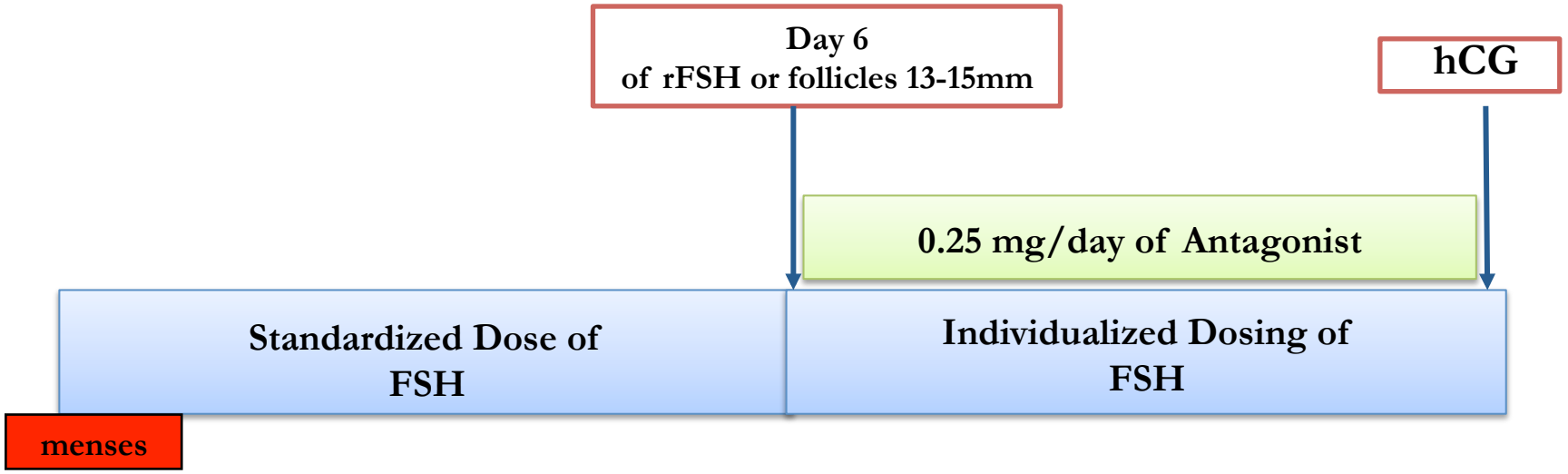
Long Protocol/GnRH agonists



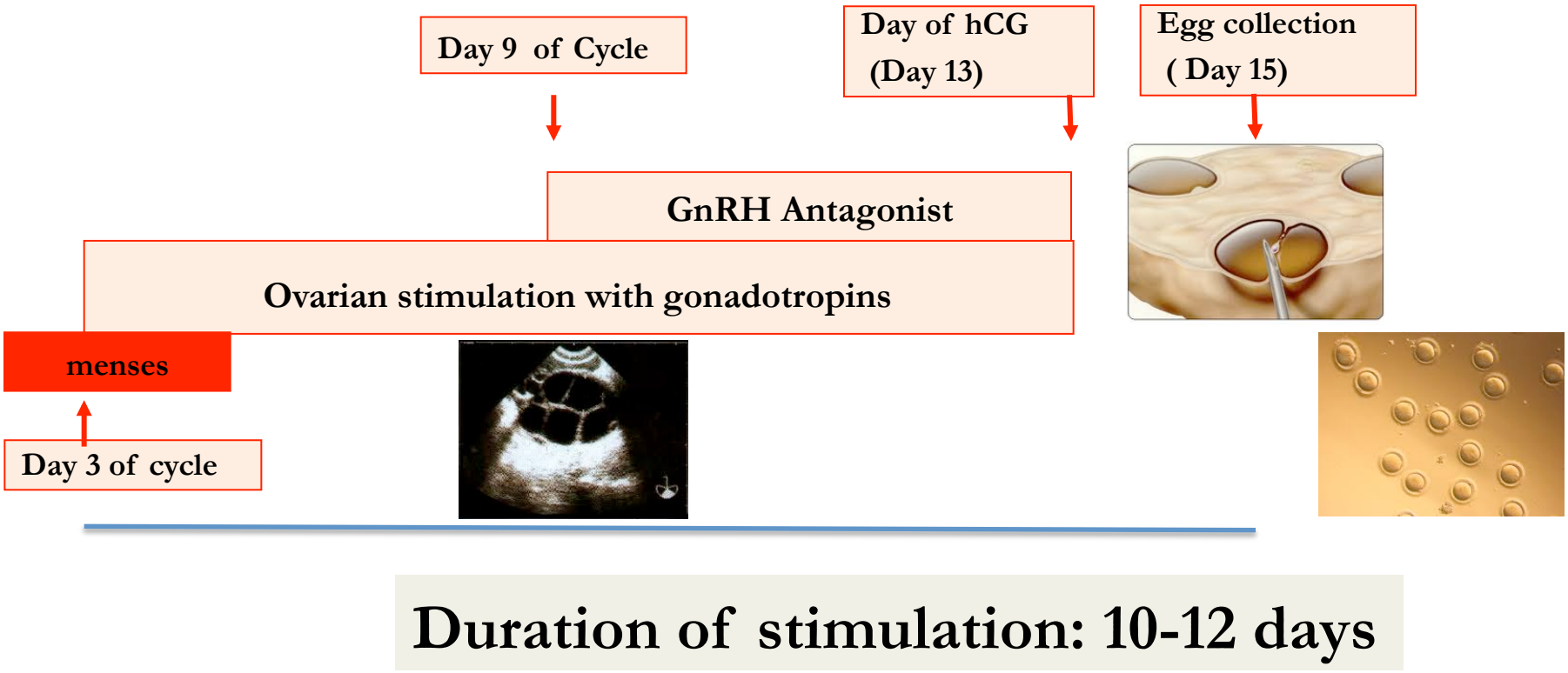
Short Flare Protocol/GnRH agonists



GnRH antagonist protocol

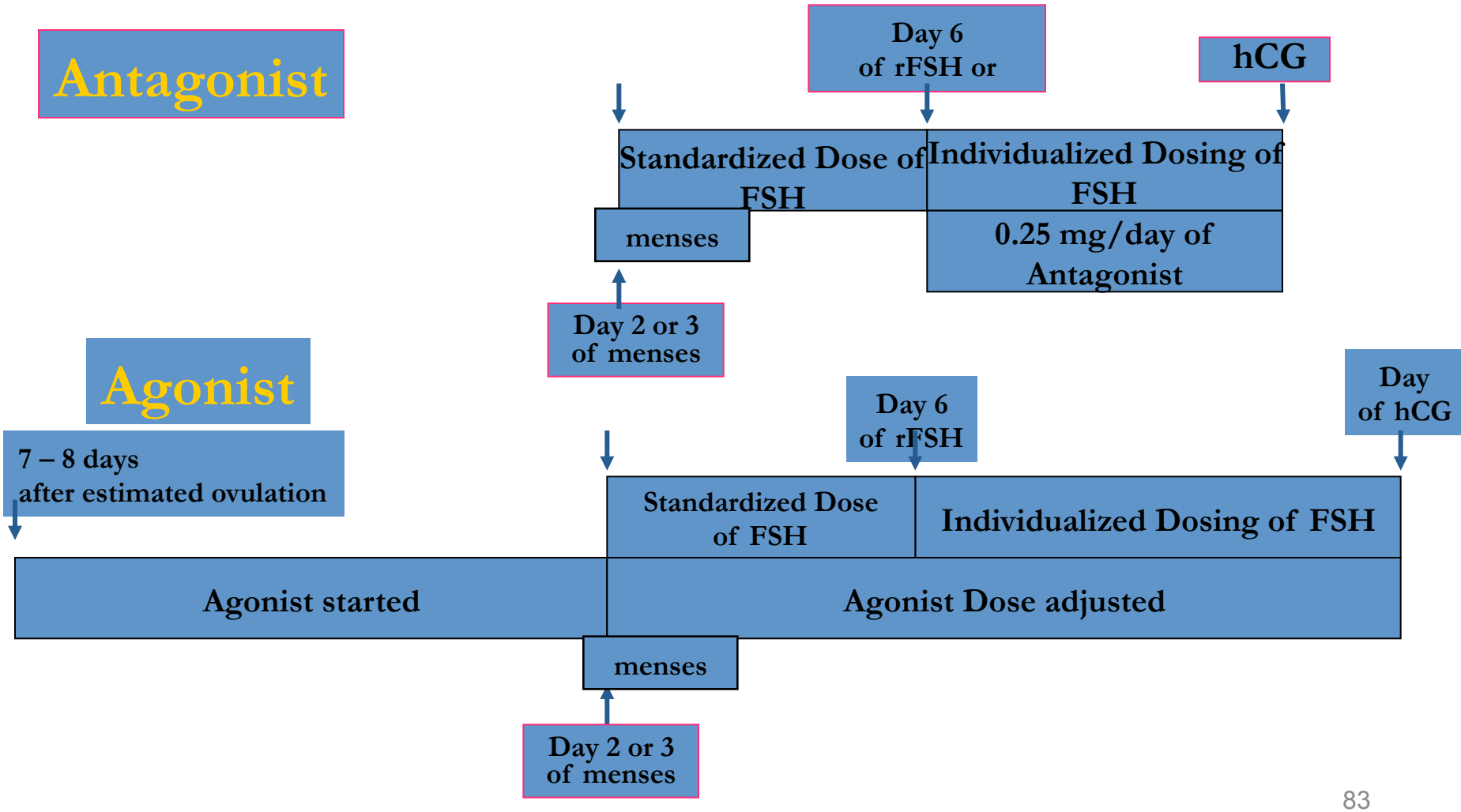


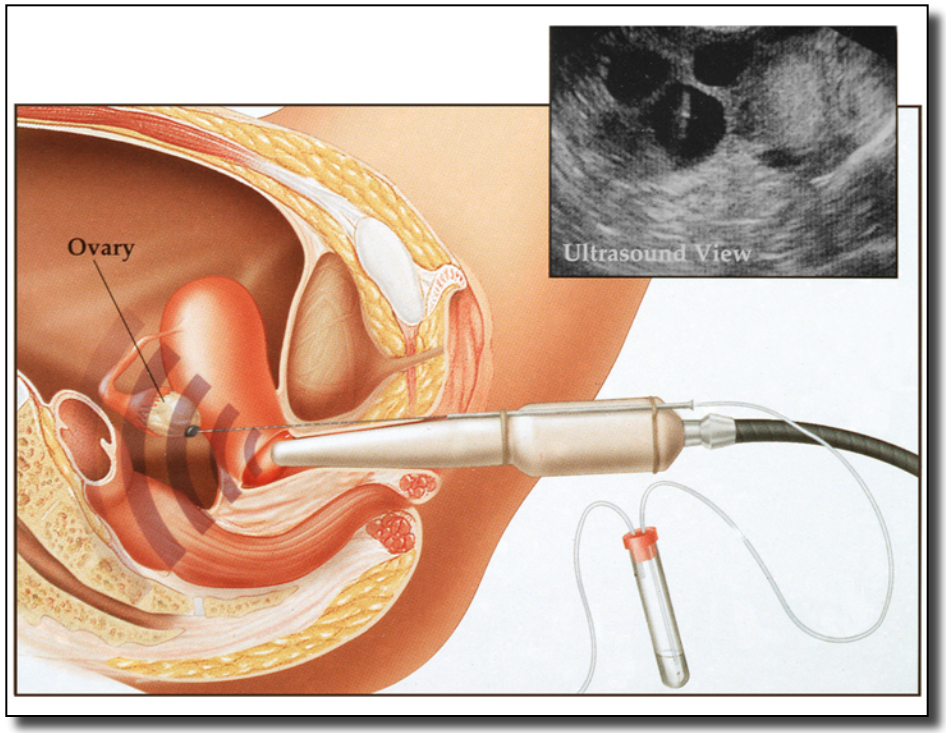
Ovarian stimulation

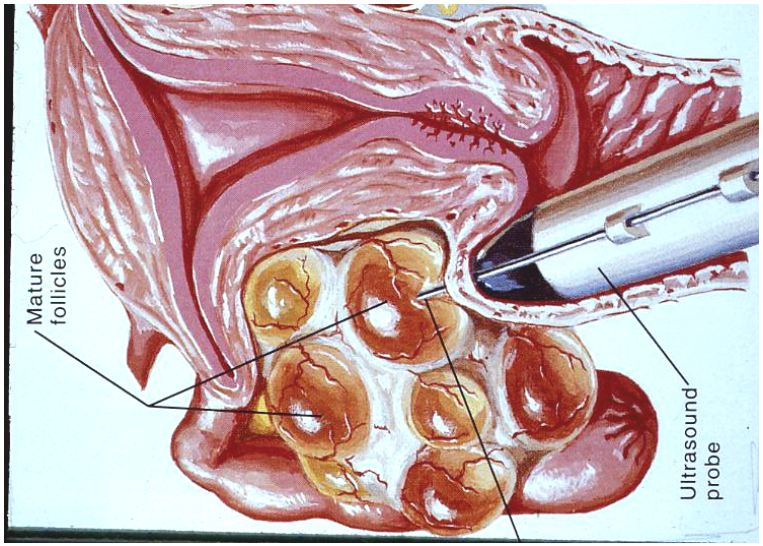


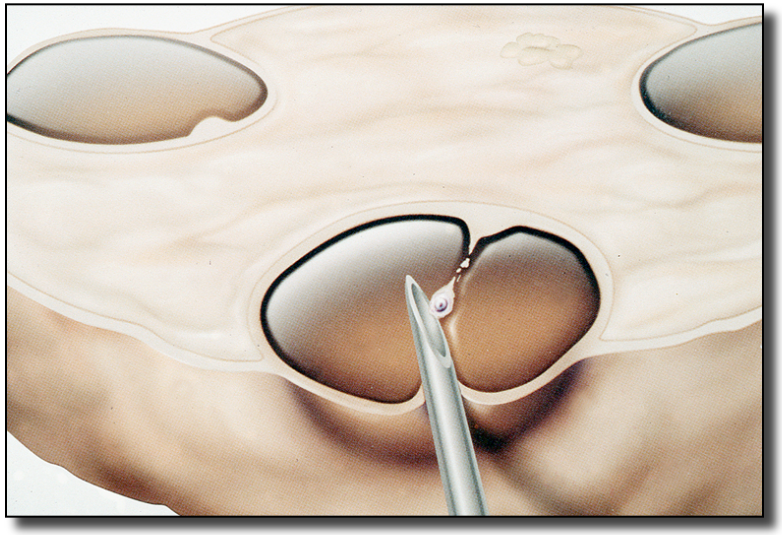
Duration of stimulation: 10-12 days

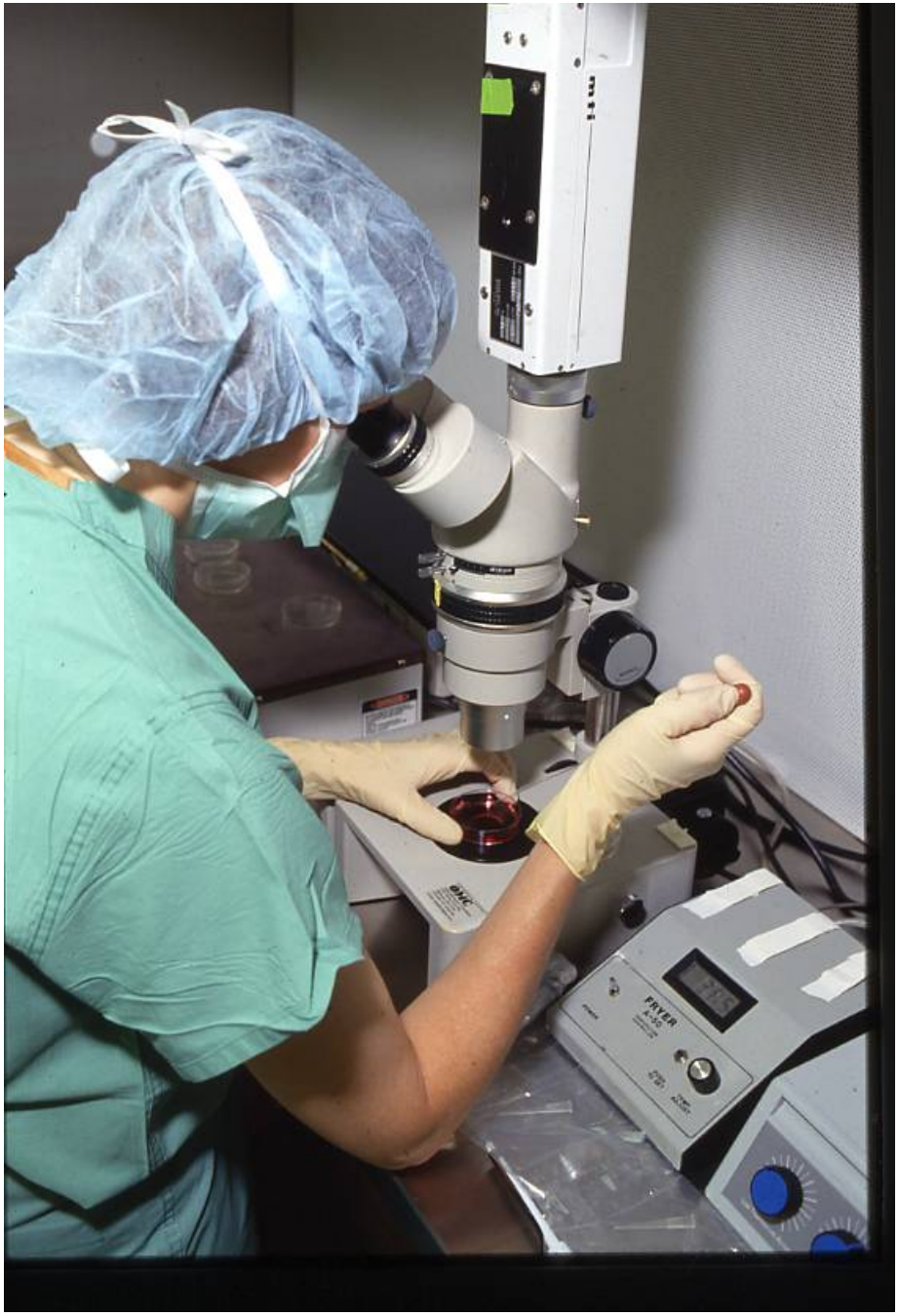
GnRH agonists vs antagonists protocol

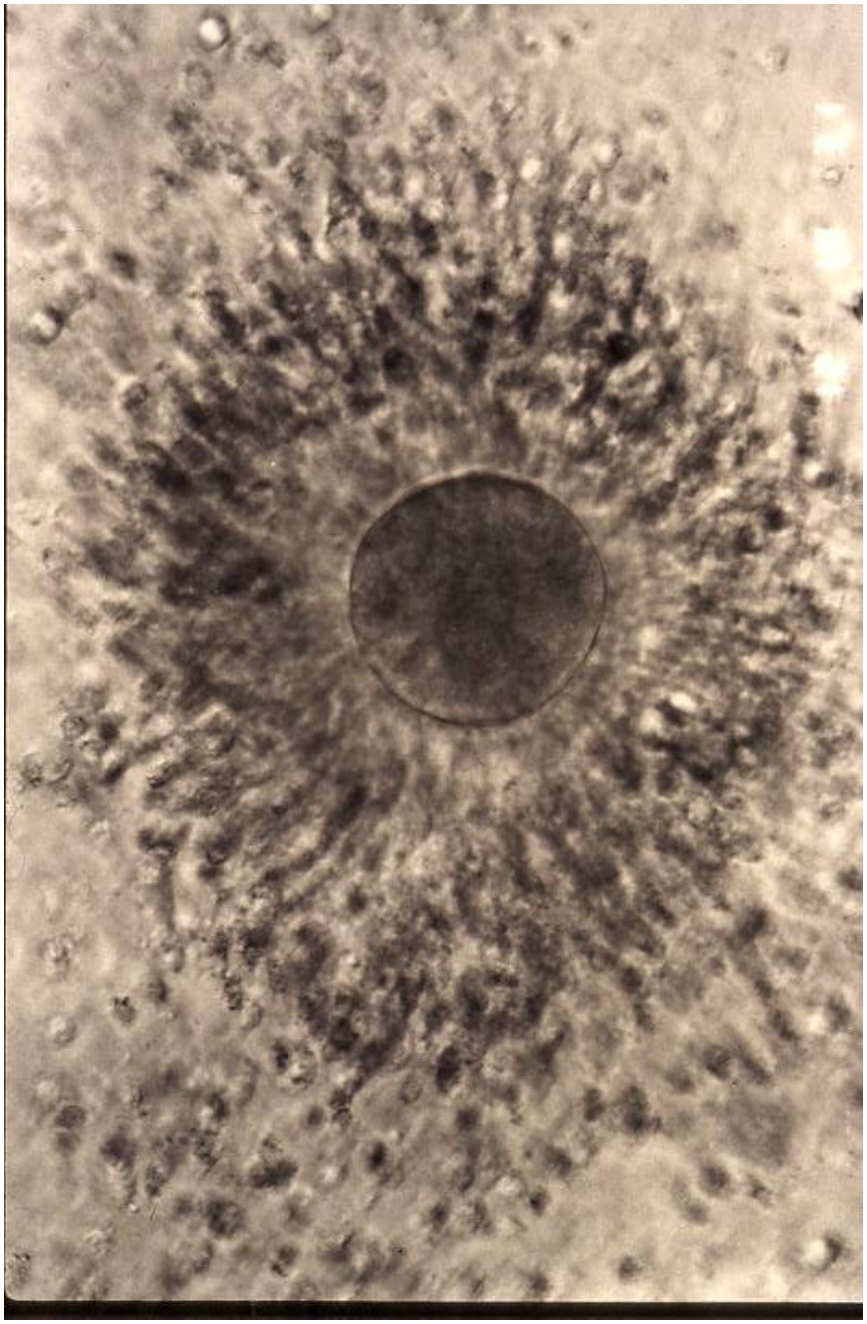


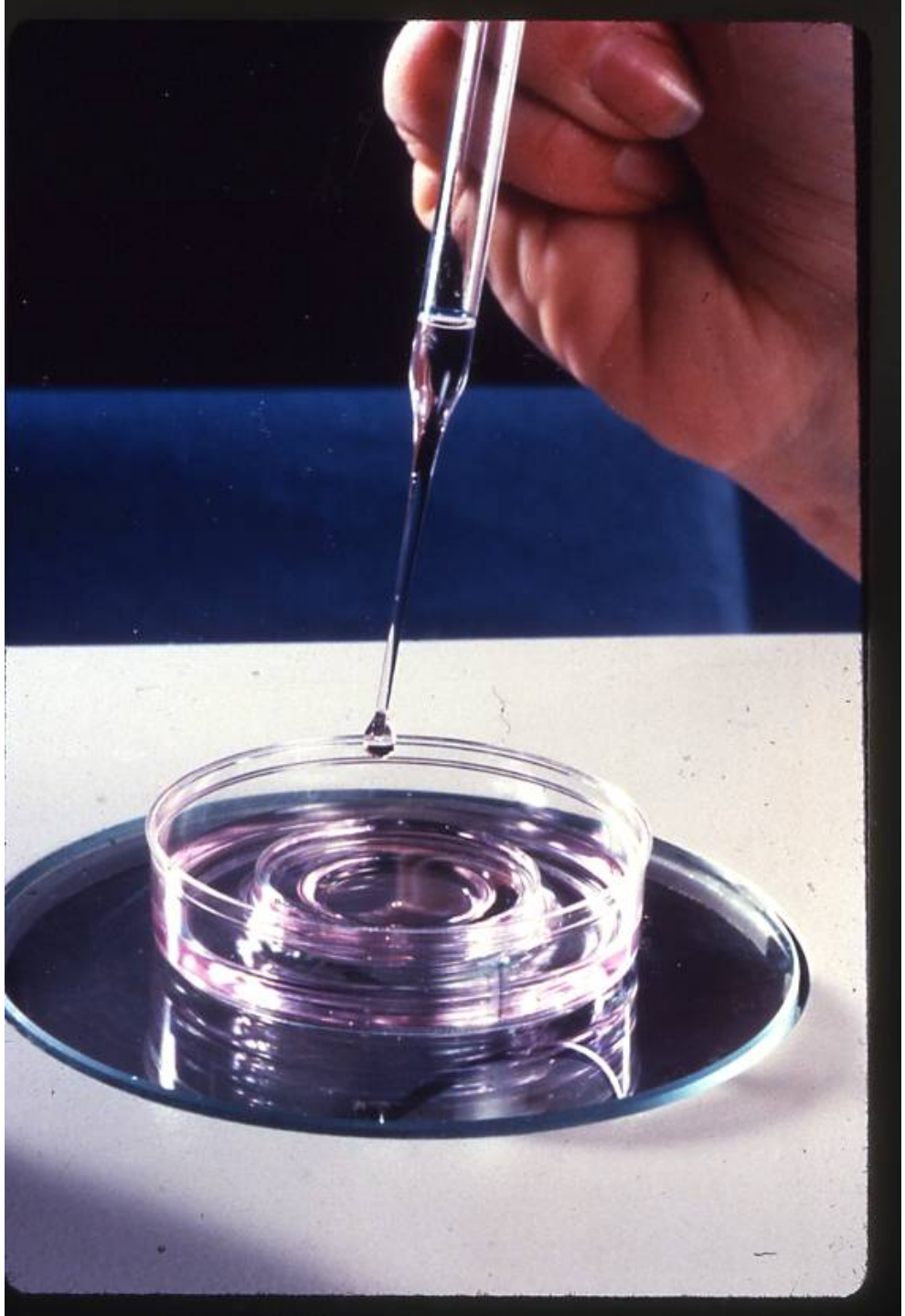

Ovary
Ultrasound View

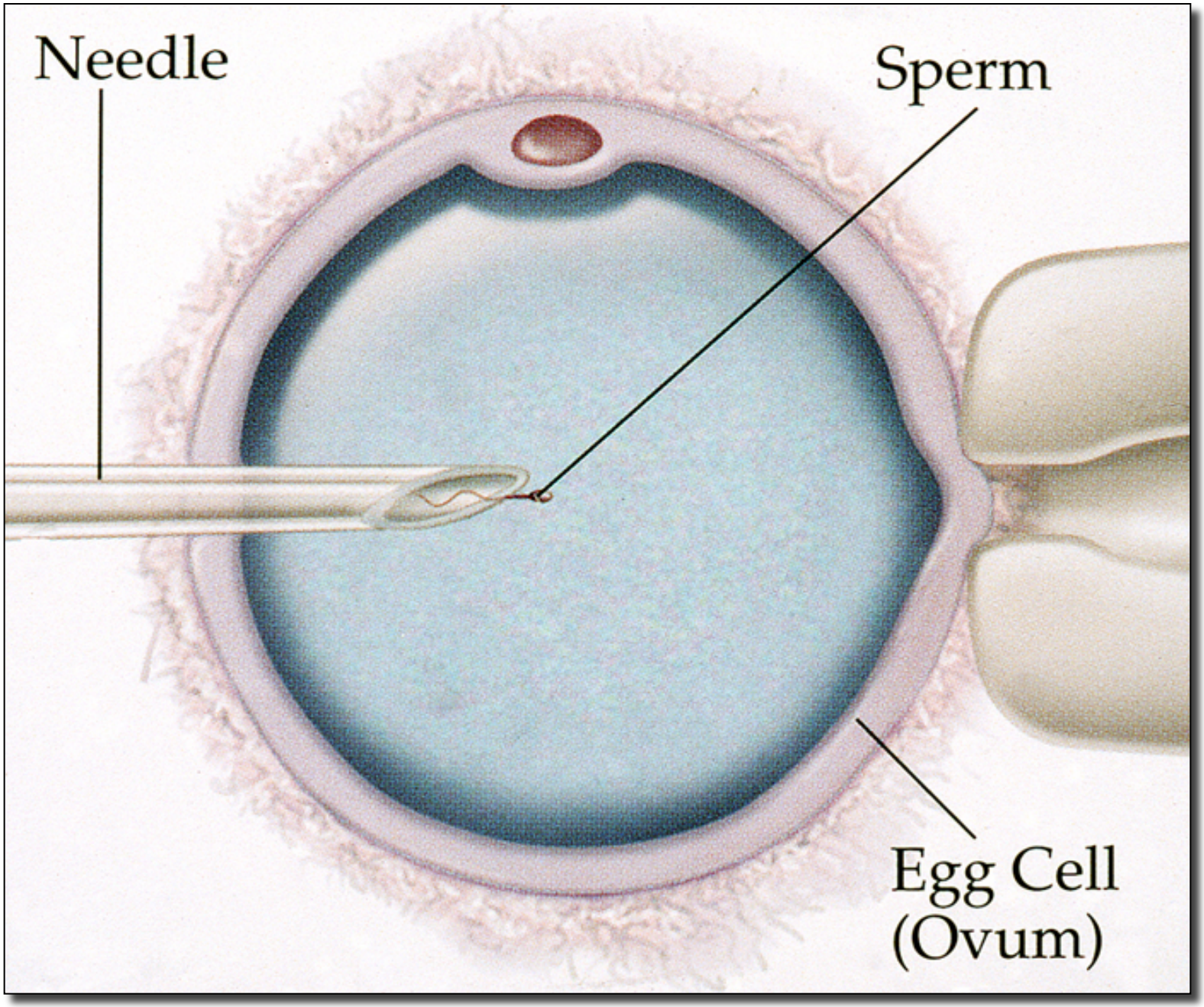

Mature follicles
Ultrasound probe

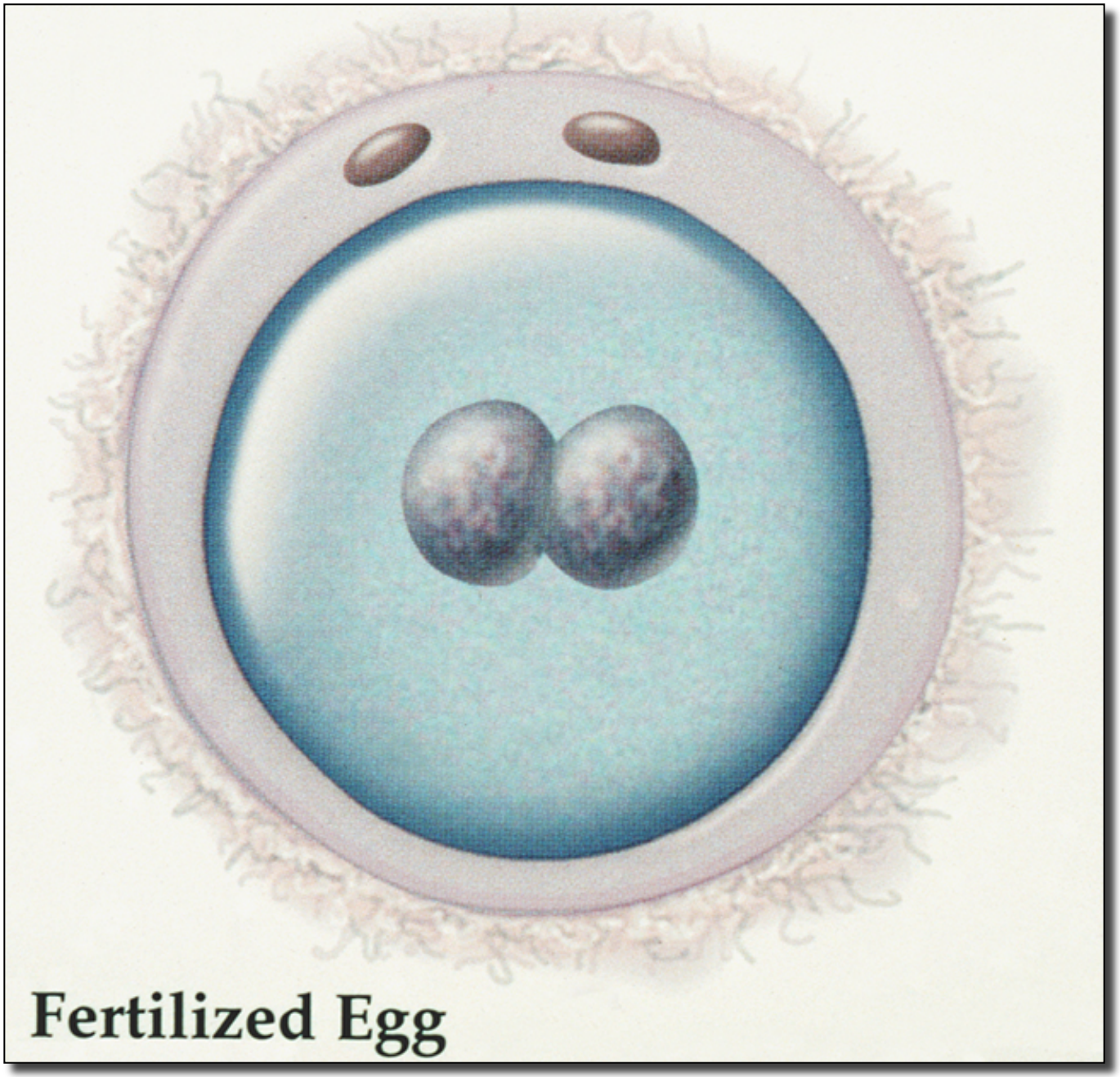



FRYER

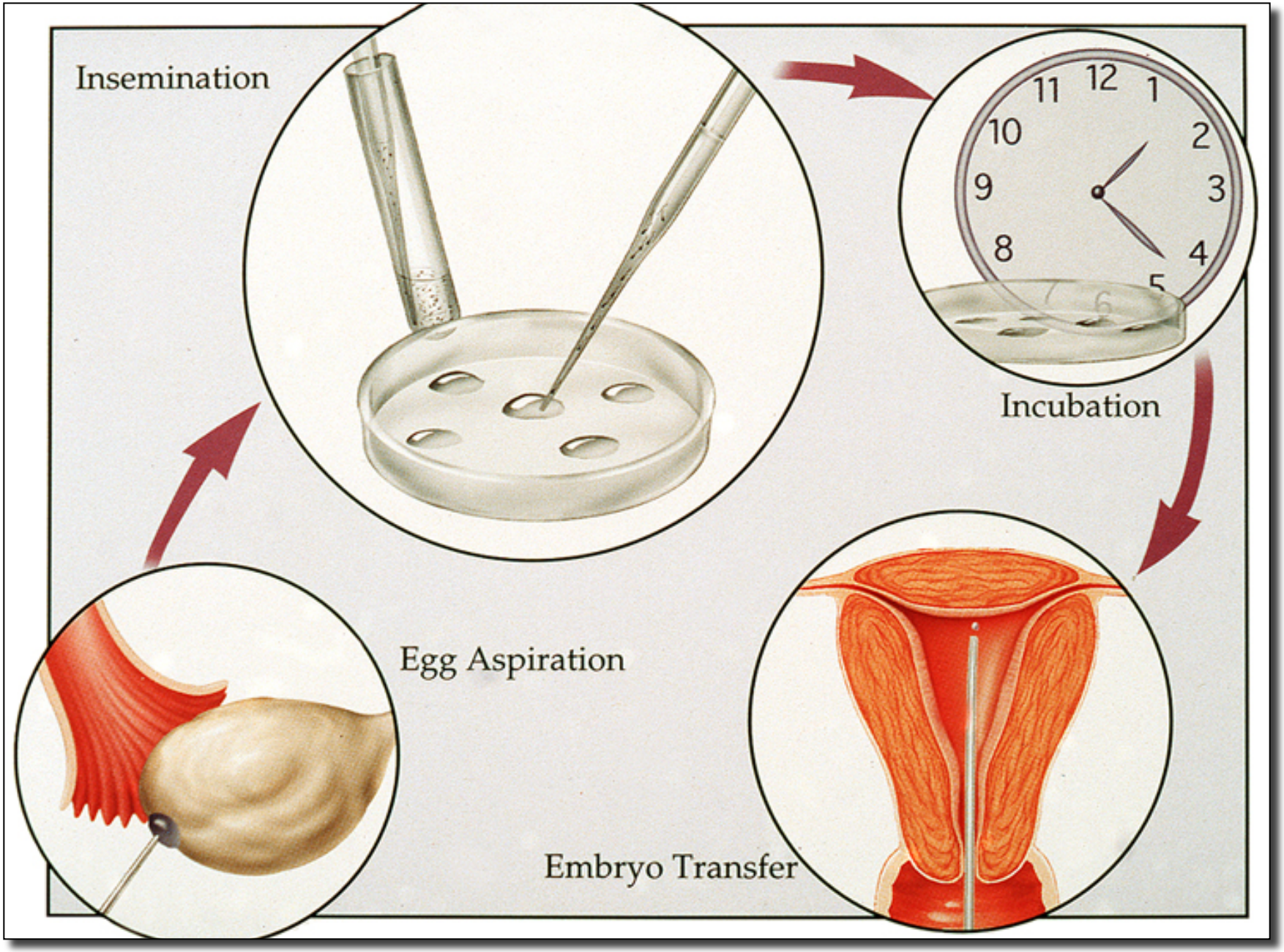





Needle
Sperm
Egg Cell
(Ovum)



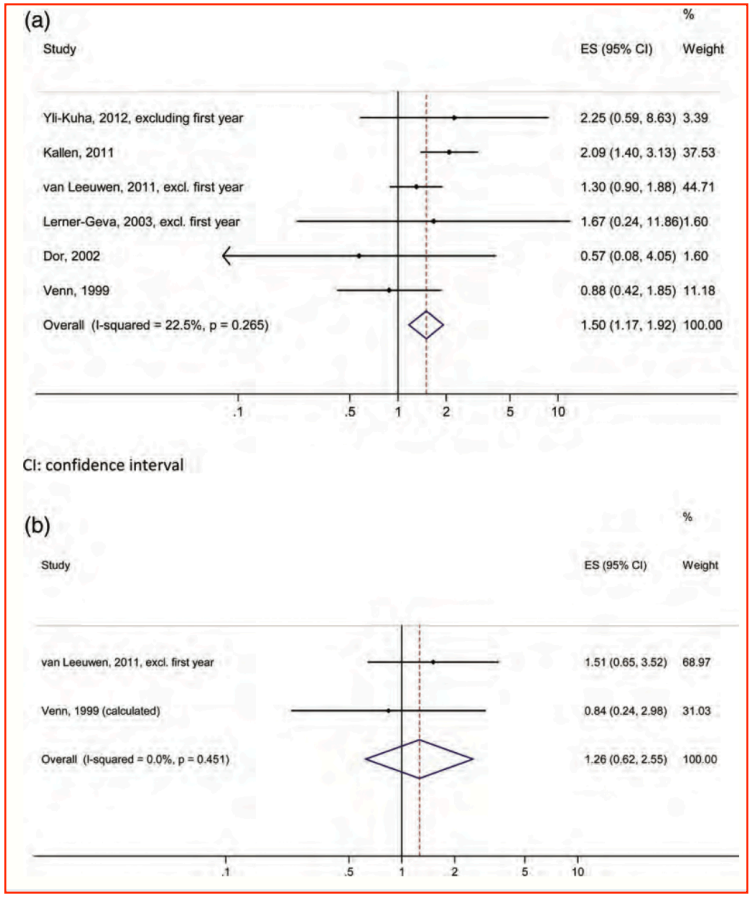
Fertilized Egg


Insemination
Incubation
Egg Aspiration
Embryo Transfer

Human Reproduction Update, Vol.19, No.2 pp. 105–123, 2013
Advanced Access publication on December 18, 2012 doi:10.1093/humupd/dms051

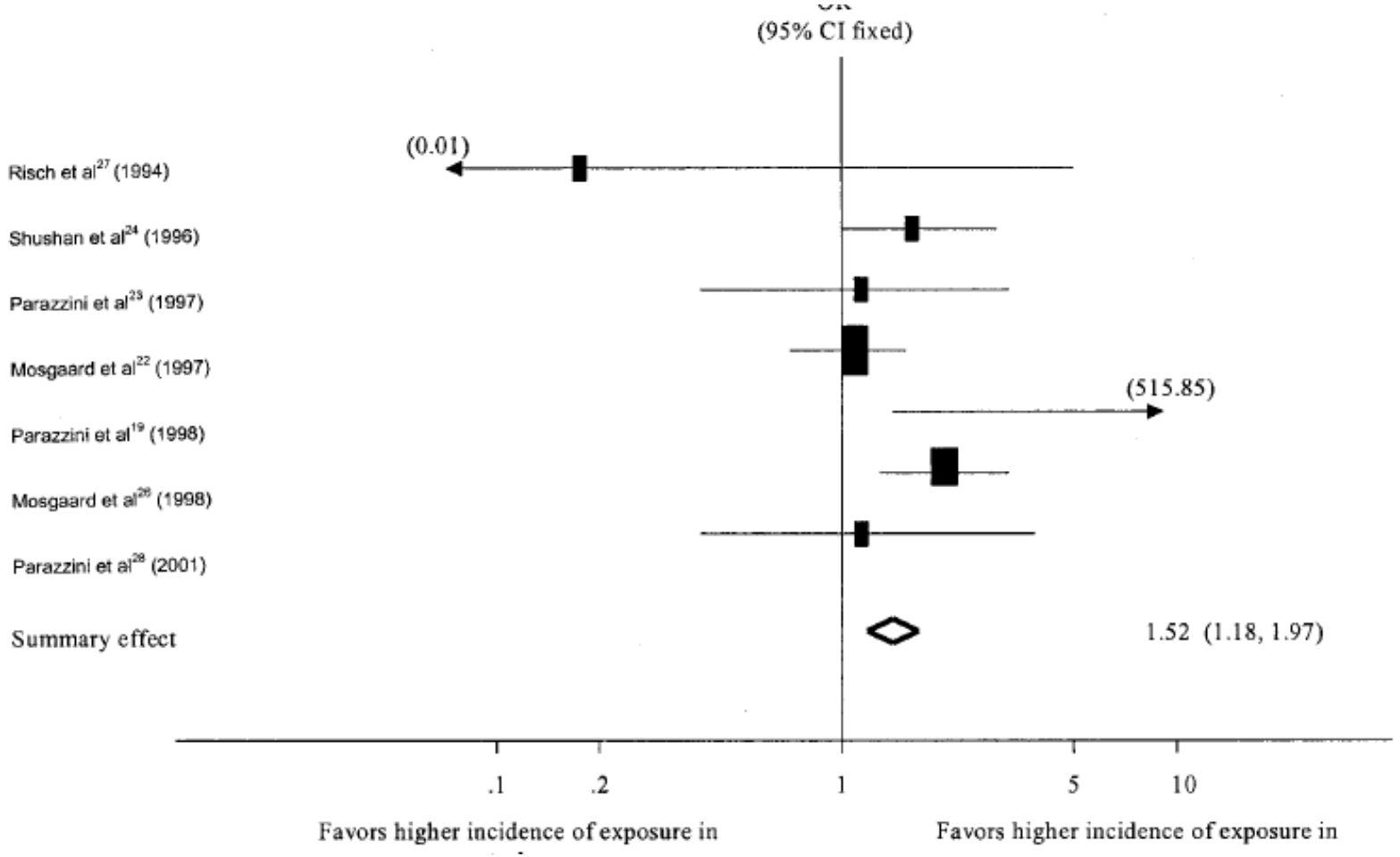
human reproduction update

Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis



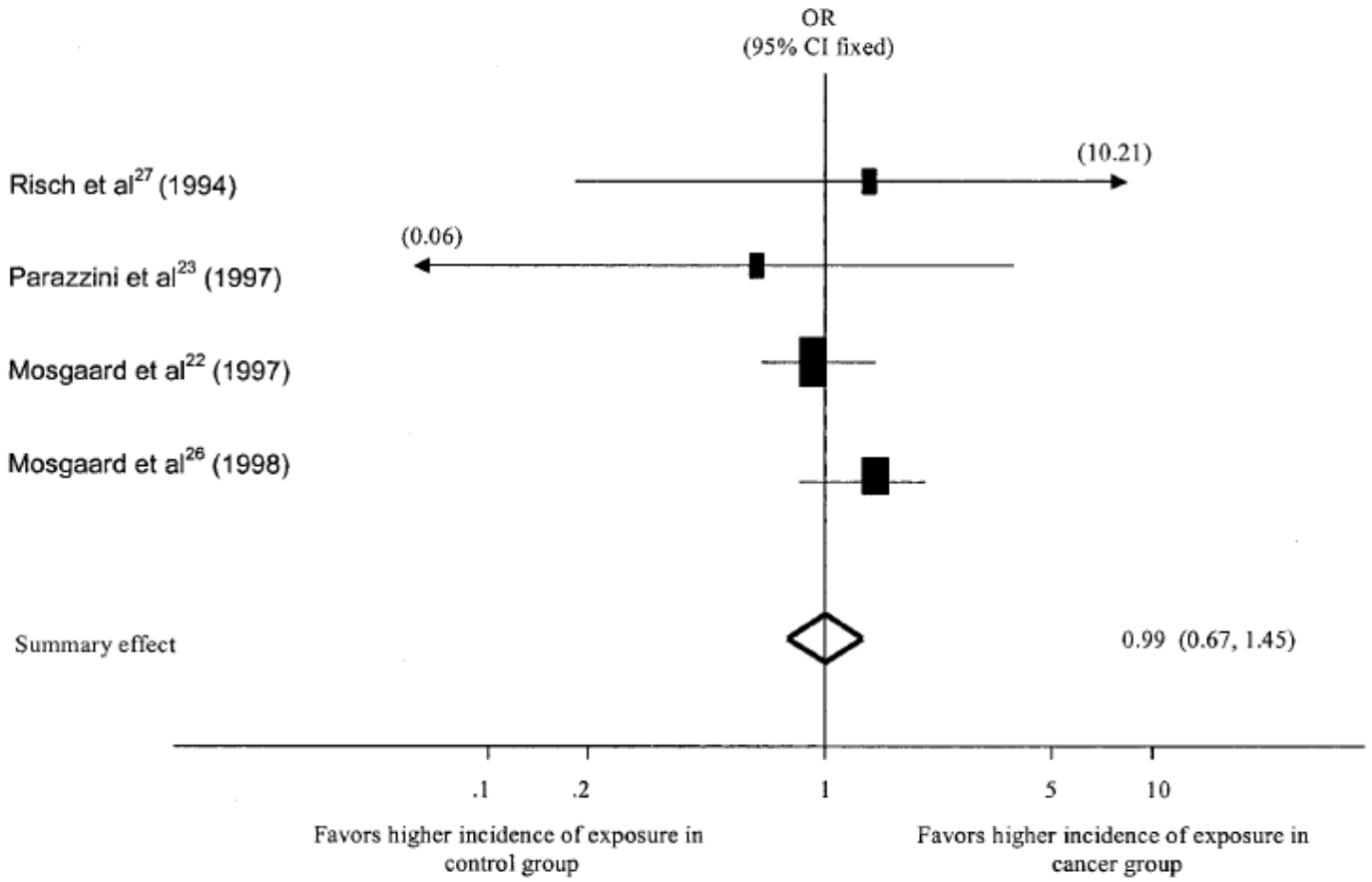
Cervical cancer

Ovarian Cancer



Kashyap et al. Obstet. Gynecol. 2004

Ovarian Cancer



Kashyap et al. Obstet. Gynecol. 2004

Ovarian Cancer

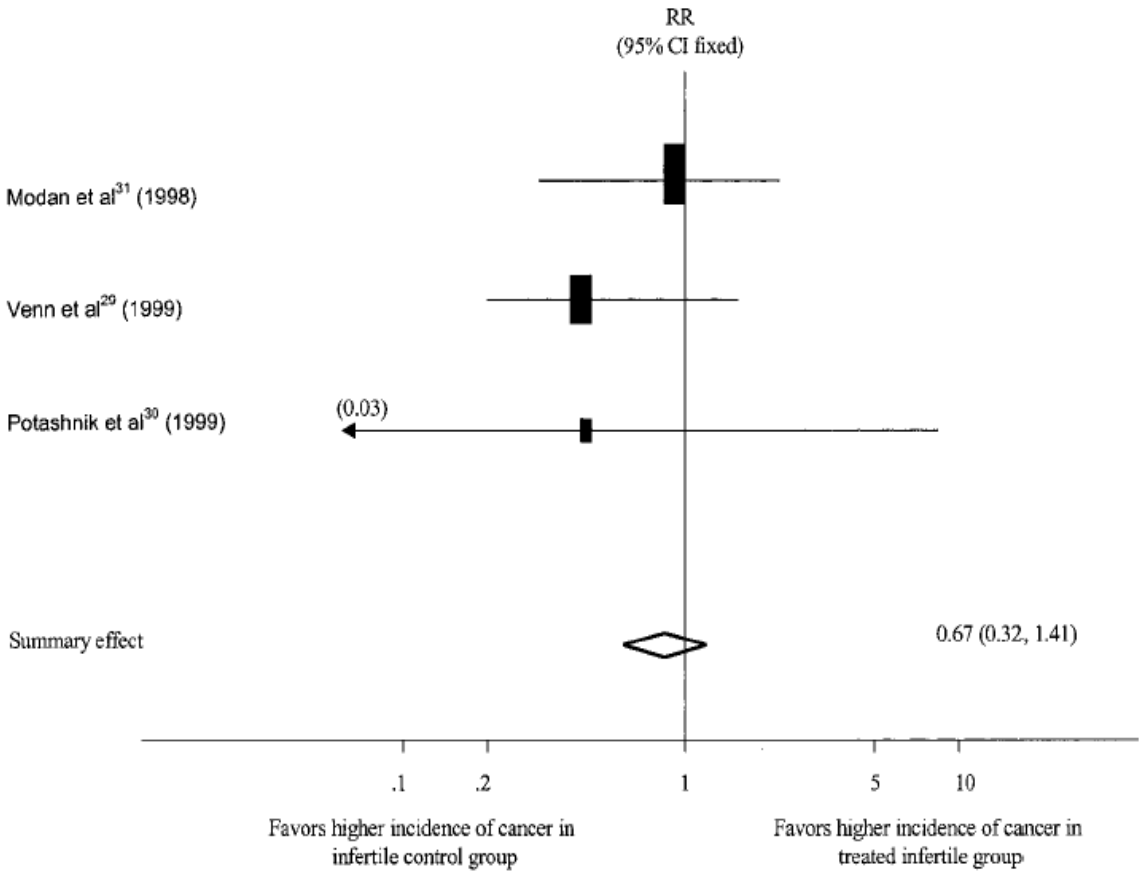


Figure 3. Comparison of ovarian cancer in treated versus untreated (control) infertile patients: cohort studies. RR = relative risk; CI = confidence interval.

Kashyap. ART and the Incidence of Ovarian Cancer. Obstet Gynecol 2004.

Kashyap et al. Obstet. Gynecol. 2004

Fertility drug use and the risk of ovarian tumors in infertile women: a case-control study

Albert Asante, M.D., M.P.H., Phoebe H. Leonard, M.D., Amy L. Weaver, Ellen L. Goode, Ph.D., M.P.H.,

TABLE 3

Association between history of infertility and ovarian tumor, stratified by gravidity.

Subgroups defined by gravidity[a]	History of infertility	Controls N (%)	Cases N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All women	No	690 (79.1)	802 (78.0)	Reference	Reference
	Yes	182 (20.9)	226 (22.0)	1.07 (0.86, 1.33)	0.99 (0.78, 1.26)[b]
Nulligravid women	No	29 (59.2)	49 (46.7)	Reference	Reference
	Yes	20 (40.8)	56 (53.3)	1.66 (0.83, 3.29)	1.65 (0.80, 3.43)[c]
Gravid women	No	656 (80.3)	753 (81.6)	Reference	Reference
	Yes	161 (19.7)	170 (18.4)	0.92 (0.72, 1.17)	0.90 (0.69, 1.16)[b]

TABLE 4

Odds ratios for ovarian tumor associated with use of fertility drugs among women with a history of infertility, stratified by gravidity.

Subgroups defined by gravidity[a]	Fertility drug use	Controls N (%)	Cases N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All	No	138 (75.8)	188 (83.2)	Reference	Reference
	Yes	44 (24.2)	38 (16.8)	0.63 (0.39, 1.03)	0.64 (0.37, 1.11)[b]
Nulligravid women	No	16 (80.0)	49 (87.5)	Reference	Reference
	Yes	4 (20.0)	7 (12.5)	0.57 (0.15, 2.21)	0.59 (0.14, 2.52)[c]
Gravid women	No	122 (75.8)	139 (81.8)	Reference	Reference
	Yes	39 (24.2)	31 (18.2)	0.70 (0.41, 1.19)	0.69 (0.37, 1.26)[b]

Note: OR = odds ratio; CI = confidence interval.

[a] Information on gravidity was not provided by one control.

[b] Adjusted for age, race, duration of oral contraceptive use, number of pregnancies, number of live births, and family history of ovarian cancer.

[c] Adjusted for age, race, duration of oral contraceptive use, and family history of ovarian cancer.

Asante. Fertility drug use and ovarian tumors. Fertil Steril 2013.

Fertil Steril. 2013;99:2031–6.

Human Reproduction, Vol.28, No.10 pp. 2813–2821, 2013
Advanced Access publication on August 13, 2013 doi:10.1093/humrep/det323

human reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

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

We excluded from analysis 15 patients with missing information on a cancer diagnosis date, 111 with ,1 year of follow-up and 60 with a hyster- ectomy during the first year of follow-up, leaving 9832 analytic study subjects and 259 346 person-years of follow-up. Person-years reflected the trunca- tion of follow-up for 1362 patients with a hysterectomy 1 or more years after initial follow-up, with 8.4% having a hysterectomy 1 – 5 years, 13.1% 6 – 10 years, 17.8% 11 – 15 years, 22.7% 16 – 20 years and 38.0% 21 or more years after study entry