Cancer Risks of Ovulation Induction

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Ovulation Induction and Cancer Risk: Reason for Concern

• Increasing numbers of women delaying first childbirth
• Nearly 6.5 million women will have infertility problems in the U.S. by 2025
• Numbers of women treated annually in the U.S. with fertility drugs has nearly doubled between 1973 and 1991
• Biologically plausible relationship with a variety of cancers
• Nulliparity is a risk factor for ovarian, breast and endometrial cancers
• Evidence that the association is largely attributable to infertility
• Effects of causes of infertility and treatment effects poorly understood
Drugs Prescribed for the Treatment of Infertility

- Clomiphene citrate
  - Well recognized selective estrogen receptor modulator
- Gonadotrophins (hMG, e.g., Pergonal, Humegon, Metrodin and FSH)
  - Contains FSH and LH
Biological Effects of Drugs Commonly Used to Treat Infertility

- Effective at inducing ovulation, a recognized risk factor for both ovarian and breast cancer
- Raise estradiol and progestin levels
Ovulation-Stimulating Drugs and Cancer Risk
Rationale for Concern

- First prescribed in early 1960’s, oftentimes in high dosages
- Linked to various cancers in clinical series
- Several alarming results for ovarian cancer from epidemiologic investigations
Whittemore Study: A Meta-analysis

*Am J Epidemiol 1992;136:1184*

<table>
<thead>
<tr>
<th>History of Infertility</th>
<th>Nulligravid Women</th>
<th>Gravid Women</th>
<th>All Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.0 (54)</td>
<td>1.0 (472)</td>
<td>1.0 (526)</td>
</tr>
<tr>
<td>Yes</td>
<td>2.1* (34)</td>
<td>0.9 (62)</td>
<td>1.0 (96)</td>
</tr>
<tr>
<td>No drug use</td>
<td>1.6 (22)</td>
<td>0.8 (54)</td>
<td>0.9 (76)</td>
</tr>
<tr>
<td>Drug use</td>
<td>27.0* (12)</td>
<td>1.4 (8)</td>
<td>2.8* (20)</td>
</tr>
</tbody>
</table>

*Numbers of cases shown in parentheses  *  *P<0.05*
Risk of ovarian cancer in infertile women


**Graph:**
- **Y-axis:** RR (relative risk)
- **X-axis:** Clomiphene use (Non-user, User, <12 cycles, 12+ cycles)

- **Non-user:** 2 cases
- **User:** 9 cases
- **<12 cycles:** 3 cases
- **12+ cycles:** 5 cases

#s of cases in yellow
Subsequent case-control studies have mainly failed to support an effect of fertility drugs on ovarian cancer risk.

However, such studies are limited by:

- Few infertile women, fewer who use infertility drugs
- Patient reports of drug exposure
- Lack of information on causes of infertility
Cohort Studies Finding No Impact of Infertility Drugs on Ovarian Cancer Risk

- Cohorts in Israel (12), Australia (13), Britain (6), and the Netherlands (15)
  (ovarian cancer #s shown in parentheses)
  - Short follow-up times
  - Incomplete information on other ovarian cancer predictors (including parity and causes of infertility)
Retrospective Cohort Study of Women Evaluated and Treated for Infertility

- 12,193 patients
- Detailed medical record abstraction
- Death certificates
- Questionnaires
- Registry linkage
- Cancer validation

- Treatment regimens
- Varying causes of infertility (e.g., endometriosis, anovulation)
- Potential confounders (e.g., parity)
## Criteria for Assigning Infertility Causes

<table>
<thead>
<tr>
<th>Endometriosis</th>
<th>Anovulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Evidence of endometriosis on pelvic laparoscopy, culdoscopy or laparotomy</td>
<td>■ Clinical history (&lt;4 periods/yr or cycle length &lt;20 or &gt;50 days)</td>
</tr>
<tr>
<td>■ Evidence of endometriosis on pelvic laparoscopy, culdoscopy or laparotomy</td>
<td>■ Progesterone withdrawal test or sella turcica exam</td>
</tr>
<tr>
<td>■ Evidence of endometriosis on pelvic laparoscopy, culdoscopy or laparotomy</td>
<td>■ Serum prolactin &gt;25 ng/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tubal disorders/pelvic adhesions</th>
<th>Male Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Obstructed or non-filling tubes on hysterosalpingogram or women with tubal obstruction, pelvic adhesions or pelvic TB on laparotomy or endoscopy</td>
<td>■ &lt;20 or &gt;300 x 10^6 sperm/ml</td>
</tr>
<tr>
<td>■ Obstructed or non-filling tubes on hysterosalpingogram or women with tubal obstruction, pelvic adhesions or pelvic TB on laparotomy or endoscopy</td>
<td>■ Progressive motility &lt;25%</td>
</tr>
<tr>
<td>■ Obstructed or non-filling tubes on hysterosalpingogram or women with tubal obstruction, pelvic adhesions or pelvic TB on laparotomy or endoscopy</td>
<td>■ Normal morphology &lt;30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cervical disorder</th>
<th>Uterine disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ 3 post-coital tests at time of ovulation not showing motile sperm</td>
<td>■ Evidence of developmental abnormality or myomas on laparoscopy, culdoscopy, laparotomy or hysteroscopy</td>
</tr>
<tr>
<td>■ Congenital absence of cervix</td>
<td>■ Evidence of developmental abnormality or myomas on laparoscopy, culdoscopy, laparotomy or hysteroscopy</td>
</tr>
<tr>
<td>■ Cervical conization</td>
<td>■ Evidence of developmental abnormality or myomas on laparoscopy, culdoscopy, laparotomy or hysteroscopy</td>
</tr>
</tbody>
</table>
Endometriosis and Ovarian Cancer

Relative Risks

1.9  
(0.9-1.4)  
3.1  
(1.5-6.8)  

No Yes

Among women with primary infertility  
(relative to women with secondary infertility)
Patients with Medical Documentation of Exposure to Infertility Drugs:

**U.S. Retrospective Cohort Study**

- **Clomiphene citrate**: 39%
- **Gonadotrophins**: 10%
Clomiphene and Ovarian Cancer


Cycles of use

Years since 1st use

Ever <6 6-11 12+ <15 15+

Cycles of use

0.8 (15) 0.9 (10) 0.5 (2) 1.6 (3) 0.5 (5) 1.6 (9)
Ovarian Cancer Summary
Long-term Impact of Fertility Drugs

Cannot rule out possibility of increase after long latency period

• Not significant, few cases exposed
• Biologically plausible
  ➢ Slow growing tumor
  ➢ Incessant ovulation
  ➢ Increased gonadotrophin levels
Research on Infertility Drugs and Breast Cancer Risk

- Biologic rationale for studying relationship
- Common condition, but exposure assessment and control for confounding factors complicate interpretation of results
- Both case-control and cohort studies
Risk of Breast Cancer Associated with Clomiphene Use in Infertile Women

Rossing et al, Gynecol Oncol 1996;60:3.

The graph shows the number of cases exposed to clomiphene in different cycles of use compared to non-users. The x-axis represents the cycles of use (Non-user, User, 1-5, 6-11, 12+), and the y-axis represents the number of cases exposed (0.1 to 1.0).

- Non-user: 12 cases
- User: 15 cases
- 1-5 cycles: 7 cases
- 6-11 cycles: 4 cases
- 12+ cycles: 4 cases

The bars are colored in yellow.
Risk of Breast Cancer Associated with Clomiphene


![Graph showing risk of breast cancer associated with clomiphene use. The x-axis represents cycles of use and years since first use, while the y-axis represents the risk ratio (with error bars).](image-url)
Breast Cancer Risk and Infertility Treatment: Results from the French E3N Cohort Study


• 92,555 women, 2,571 invasive breast cancers
• Exposure information self reported, no information on indications for drug usage
• RRs mainly in the range of 0.94-0.99
• Only increased risk for treatment among those with a family history of breast cancer (RRs 2.32-2.77), based on small #s
Retrospective Cohort Study of 5,788 Women Attending Infertility Clinics in Israel


- IVF Cohort; 131 breast cancers; other risk factor information obtained from medical records
- Significantly elevated risk associated with clomiphene (SIR=1.4, 95% CI 1.0-1.8)
- Similar results based on internal analyses and a nested case-control study (OR=2.7, 95% CI 1.3-5.7)
### Clomiphene & Breast Cancer Among Women with Ovulatory Infertility, Nurses’ Health Study II, 1993-2001

*Terry et al, Arch Intern Med 2006;166:2484.*

<table>
<thead>
<tr>
<th>Clomiphene, mo</th>
<th># Cases</th>
<th>HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>29</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>12</td>
<td>0.47</td>
<td>(0.23-0.97)</td>
</tr>
<tr>
<td>2.5 - 5</td>
<td>6</td>
<td>0.46</td>
<td>(0.18-1.15)</td>
</tr>
<tr>
<td>6 - 10</td>
<td>10</td>
<td>0.49</td>
<td>(0.22-1.06)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>4</td>
<td>0.25</td>
<td>(0.09-0.75)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
Breast Cancer Risk After Fertility Drugs: a Large Danish Cohort (n=54,362) Study


RRs
3.5
3
2.5
2
1.5
1
0.5
0

Gonadotrophins | Clomiphene | hCG | GnRH | Progesterone

331 breast cancers

No use | Use
Fertility Drugs and Breast Cancer Risk

- Inconsistent results across studies
- Need for additional studies to monitor long-term effects
- Results will need to carefully document exposures and indications for usage
Breast Cancer: Biologic Plausibility of Findings

- Drug use increases endogenous hormones
- Parallel with follow-up of a cohort of mothers exposed to DES during pregnancy

RR=1.27 (95% CI 1.07-1.52)

Infertility Drugs and Endometrial Cancer in a Cohort of Israeli Women


The bar chart shows the prevalence of endometrial cancer cases among women exposed to different infertility drugs. The categories include:

- Untreated
- Treated
- Clomiphene
- Clomiphene + Gonadotrophins

The number of cases exposed in each category is as follows:

- Untreated: 8 cases
- Treated: 13 cases
- Clomiphene: 7 cases
- Clomiphene + Gonadotrophins: 4 cases

The acronym SIR stands for "Standardized Incidence Ratio."
Risk of Endometrial Cancer Associated with Clomiphene


<table>
<thead>
<tr>
<th>Years since first use</th>
<th>Ever</th>
<th>&lt;10</th>
<th>10-19</th>
<th>20+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.8</td>
<td>1.2</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>(19)</td>
<td>(4)</td>
<td>(9)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

$P_{\text{trend}}=0.05$
Clomiphene is a SERM

- Acts as an antiestrogen on hypothalamus
- Action on endometrium may be
  - Direct, similar to tamoxifen
  - Indirect, increasing unopposed estrogen levels early in menstrual cycle
Mechanism of Action of Ovulation
Stimulating Drugs

• Hyper-ovulation
  ❖ Ovarian cancer (and to lesser extent) breast cancer
• Increases in estrogen and progestin levels
  ❖ Breast and endometrial cancer, possibly other hormonally-related cancers
Future Directions of Research on Ovulation Stimulating Drugs and Cancer Risk

- Need for large studies
- Evaluation of long-term effects
- Drug exposures and indications for use need to be carefully documented
- Additional studies of newer clinical modalities
- Assessment of other hormonally-related cancers