Endometrial Cancer and Contraception

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5. Outlook: Research on mechanisms of hormonal (progestogen) action to assess endometrial safety

Alfred O. MUECK; MD. Pharm.D. PhD. 
1) University Hospitals of Tuebingen, Germany 
2) Beijing OB/GYN Hospital, Capital Medical University, China 
3) ZheJiang University (Hangzhou) China

CONFLICT OF INTEREST
Sponsored by various companies (producing and/or promoting contraceptives) for lectures, advisory, research 
Board member of various societies with special interest in sexual hormones (ECC, ESG, EMAS, IMS, ISGE, CSGE) (President of the German Menopause Society)
Systematic Review (2010): COC decrease risk of endometrial cancer

Hormonal contraception and risk of endometrial cancer: a systematic review

Alfred O. Mueck, Harald Seeger and Thomas Rube

Department of Obstetrics and Gynaecology, Centre for Women’s Health, University of Munich, Germany.

Correspondence should be addressed to: T. Rube, Obstetrics, Klinik fur Frauenheilkunde, Marchioninistrasse 15, D-81377 Munich, Germany.

Mueck AO et al. Endocrine Related Cancer 2010; 17: 263-271

Relevant studies COC chronologically: RR, investigated factors

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Case Numbers</th>
<th>Controls Numbers</th>
<th>RR (95% CI)</th>
<th>Statistic</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Number of enrolled patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueck AO</td>
<td>2010</td>
<td>27,276</td>
<td>115,743</td>
<td>0.74 (0.67-0.81)</td>
<td>3.82E-12</td>
<td>27,276</td>
<td>115,743</td>
<td>17,101,207</td>
</tr>
<tr>
<td>Collaborative Group</td>
<td>2015</td>
<td>27,276</td>
<td>115,743</td>
<td>0.74 (0.67-0.81)</td>
<td>3.82E-12</td>
<td>27,276</td>
<td>115,743</td>
<td>17,101,207</td>
</tr>
</tbody>
</table>

Last meta-analysis (2015): COC decrease risk of endometrial cancer

Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27,276 women with endometrial cancer from 36 epidemiological studies


Total women included: 27,276 cases / 115,743 controls

Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27,276 women with endometrial cancer from 36 epidemiological studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Number of enrolled patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>27,276</td>
<td>115,743</td>
<td>17,101,207</td>
</tr>
</tbody>
</table>

Total 27,276 cases / 115,743 controls

15 Prospective studies (cases/controls)


- No reliable data on the risk of endometrial cancer using oral or injectable Progestin-only contraceptives

There were too few women with endometrial cancer who had used exclusively progestin-only oral contraceptives (56 cases), progestin-only injectable hormonal contraceptives (19 cases), combined injectable hormonal contraceptives (13 cases) or sequential oral contraceptives (11 cases) for reliable analysis.

### 11 Retrospective population studies (cases/population controls)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases/case-control</th>
<th>Number of controls/control</th>
<th>Number of cases/case-control</th>
<th>Number of controls/control</th>
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<tbody>
<tr>
<td>USA</td>
<td>402/117</td>
<td>156</td>
<td>402/117</td>
<td>156</td>
</tr>
<tr>
<td>Spain</td>
<td>46/137</td>
<td>162</td>
<td>46/137</td>
<td>162</td>
</tr>
<tr>
<td>Sweden</td>
<td>756/3132</td>
<td>3132</td>
<td>756/3132</td>
<td>3133</td>
</tr>
<tr>
<td>Norway</td>
<td>6,463/6,463</td>
<td>6,463</td>
<td>6,463/6,463</td>
<td>6,463</td>
</tr>
<tr>
<td>Italy</td>
<td>2,955/2,955</td>
<td>2,955</td>
<td>2,955/2,955</td>
<td>2,955</td>
</tr>
<tr>
<td>Canada</td>
<td>2,491/2,491</td>
<td>2,491</td>
<td>2,491/2,491</td>
<td>2,491</td>
</tr>
<tr>
<td>Austria</td>
<td>5,874/5,874</td>
<td>5,874</td>
<td>5,874/5,874</td>
<td>5,874</td>
</tr>
<tr>
<td>Total</td>
<td>20,379/20,379</td>
<td>20,379</td>
<td>20,379/20,379</td>
<td>20,379</td>
</tr>
</tbody>
</table>

Collaborative Group. Lancet Oncol 2015; 1061-70

### 10 Retrospective hospital studies (cases/hospital controls)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases/case-control</th>
<th>Number of controls/control</th>
<th>Number of cases/case-control</th>
<th>Number of controls/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>32/292</td>
<td>292</td>
<td>32/292</td>
<td>292</td>
</tr>
<tr>
<td>Spain</td>
<td>76/1,242</td>
<td>1,242</td>
<td>76/1,242</td>
<td>1,242</td>
</tr>
<tr>
<td>Norway</td>
<td>5,375/5,375</td>
<td>5,375</td>
<td>5,375/5,375</td>
<td>5,375</td>
</tr>
<tr>
<td>Italy</td>
<td>321/321</td>
<td>321</td>
<td>321/321</td>
<td>321</td>
</tr>
<tr>
<td>Canada</td>
<td>2,576/2,576</td>
<td>2,576</td>
<td>2,576/2,576</td>
<td>2,576</td>
</tr>
<tr>
<td>Austria</td>
<td>5,874/5,874</td>
<td>5,874</td>
<td>5,874/5,874</td>
<td>5,874</td>
</tr>
<tr>
<td>Total</td>
<td>13,798/13,798</td>
<td>13,798</td>
<td>13,798/13,798</td>
<td>13,798</td>
</tr>
</tbody>
</table>

Collaborative Group. Lancet Oncol 2015; 1061-70

### RR (%): Five years of use

**Prospective Studies**

- Adjusted for study (center), age, parity, BMI, smoking, type of HRT, if used

**Retrospective Studies**

- Population controls
- Hospital controls

**Summary:** After at least 5 years use of COC about 25% risk reduction

Collaborative Group. Lancet Oncol 2015; 1061-70

### RR (%): No dependency on reproductive or lifestyle factors

- No dependency on duration of use
- Decrease of endometrial cancer risk dependent on duration of use

After 10 years COC use about 60-70% risk reduction for endometrial cancer

Collaborative Group. Lancet Oncol 2015; 1061-70
Persistance of decreased endometrial cancer risk after withdrawal of COC (dependent on time since last use)

Collaborative Group. Lancet Oncol 2015; 1061-70

15 years after stop of COC still about 50% risk persisting risk reduction for endometrial cancer

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Search strategy MEDLINE since 1969; PubMed, EMBASE since 1980.
Key words contraceptives, EC, neoplasm
only originals, no abstracts, English literature up to 2009
PubMed; MEDLINE present search: progestins, POP, DMPA
è no published meta-analyses or systematic reviews

No reliable data on the risk of endometrial cancer using oral or injectable Progestin-only contraceptives

WHO Collaborative Study of Neoplasia and Steroid Contraception
Int J Cancer 1991; 49: 186-180
è no cases and only 2 controls who had used oral POPs exclusively

Swedish case-control study
è only 1/5 used the minipill (OR 0.6; 0.2-1.4)
and 0/14 DMPA

CASH Study
Gynecol Oncology 2000; 82: 233-240
è only one case and 6 controls who had used POPs exclusively:
crude OR 0.6 (95% CI 0.1-5.0)

Royal College cohort study
Hannaford PC et al. BMJ 2007; 335 (7621): 651
è only 3% were POP users, risks have not been observed

Conservative Therapy (= Progestogen-only Therapy) of atypical hyperplasia and endometrial carcinoma
– Guidelines of German Oncology Society

1. May be discussed for low-grade carcinoma (Ia, G1) for patients wanting pregnancy
2. After finalizing family planning, surgery (hysterectomy) should be performed
3. Precondition: good compliance for close surveillance regarding clinical symptoms, ultrasound and histology
4. Progestin-only therapy can be performed using
   - high-dose Medroxyprogesterone acetate (e.g.500 mg/d)
   - high-dose Megestrolacetate (e.g. 160 mg/d)
   - LNG-IUD (5 years) (MIRENA)

LNG-IUD (MIRENA) can prevent (atypical) endometrial hyperplasia and may protect from endometrial carcinoma – but more data needed!

Treatment of endometrial hyperplasia comparing LNG-IUD and oral progestins...


LNG-IUD in the treatment of endometrial hyperplasia...


Treatment of endometrial hyperplasia without atypia in peri- and postmenopausal women with LNG-IUD...

Hannaford PC et al. Maturitas 2007; 58: 425-430

LNG-IUD as therapy for endometrial carcinoma...

Ganopoulos T et al. Gynecol Oncol 2004; 93

Regression of atypical endometrial hyperplasia to adenocarcinoma despite intrauterine progestogen treatment with the LNG-IUD...

Kresovic J. Obstet Gynecol 2008; 111: 547-549
**LNG-IUD (MIRENA) can prevent**

- **endometrial protection from**
- **tamoxifen-stimulated changes**
- **in tamoxifen-treated women**

**A randomised controlled trial of prophylactic LNG-IUD in tamoxifen-treated women**

- **Chan SSC et al. BJOG 2007; 114: 1510 -1515**

**Long-term effects of LNG-IUD on the endometrium in breast-cancer patients taking tamoxifen:**

- **Kagan MD et al. Contraception 2008; 11: 252-257.**

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   - Primary risk and use for treatment of endometrial cancer
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5. **Outlook: Research on mechanisms of hormonal (progestogen) action to assess endometrial safety**

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**Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma:**

<table>
<thead>
<tr>
<th>Duration of use (years)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use</td>
<td>5403  (81.6)</td>
<td>4412 (82.7)</td>
<td>Ref</td>
</tr>
<tr>
<td>≤ 1</td>
<td>259 (3.9)</td>
<td>339 (3.5)</td>
<td>0.86 (0.68, 1.08)</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>342 (5.2)</td>
<td>502 (6.0)</td>
<td>0.86 (0.68, 1.09)</td>
</tr>
<tr>
<td>3-5</td>
<td>176 (2.7)</td>
<td>262 (2.2)</td>
<td>0.99 (0.81, 1.23)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>400 (6.0)</td>
<td>894 (8.1)</td>
<td>0.81 (0.65, 0.99)</td>
</tr>
</tbody>
</table>

**IUD: Stronger carcinop-protective effect of with longer use**

- **In the studies included in this analysis only 21 cases and 12 controls using LNG-IUD have been observed. The authors claim that future epidemiological studies are needed to investigate the association of endometrial cancer with this type of IUD.**
Pregnancies can protect from EC through shedding of precancerous cells, with no additive protective effect using IUD, in contrast to nulliparous women who lack such a mechanism.

Obesity increases the risk of EC, but IUD use does not elicit protective effect!

Smoking decreases EC risk but IUDs have no additional effect!

Diabetes increases EC risk but IUDs have no protective effect!

MHT can increase EC risk, dependent on type and dosage (not identified in this analysis).

IUD use can protect from EC risk during use of MHT.

Note: Since in this analysis LNG-IUDs have been evaluated only for 21 cases and 12 controls, the protective effect is attributable to the use of inert or copper IUDs!
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COC not only can reduce the risk for type 1, but also for type 2 endometrial carcinoma and may be (?) also for Sarcoma

Collaborative Group. Lancet Oncol 2015; 1061-70

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Controls</th>
<th>Relative risk (95% CI) for ever use of oral contraceptives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>6280</td>
<td>45435</td>
<td>1.00 (0.96-1.04)</td>
</tr>
<tr>
<td>Type I carcinoma</td>
<td>1990</td>
<td>19159</td>
<td>0.98 (0.95-1.02)</td>
</tr>
<tr>
<td>Type II carcinoma</td>
<td>408</td>
<td>3198</td>
<td>0.75 (0.67-0.82)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>179</td>
<td>4024</td>
<td>0.43 (0.36-0.5)</td>
</tr>
</tbody>
</table>

Information about histological subtype was available in 17,754 (65%) of the 27,276 cases

Note: Since the risk using LNG-IUD was not assessed in this meta-analysis the possible carcinoprotective effect is related to use of inert IUD and Copper-IUD.

Can COC reduce the risk of Type 2 endometrial cancer and of uterine sarcoma?

- 15 studies (most also in meta-analysis of Collaborative Group 2015):
  Similar sign, reduction of both type I and type II for ever use of COC!

Buellaw VW, Pike MC et al.
Type I and II endometrial cancers: have different risk factors?
J Clin Oncol 2013; 31: 2607-18

Collaborative Group (2015): COC reduce the risk of type 1 and type 2 endometrial cancer, and may be (?) also for Sarcoma

- Ever use of any COC does reduce Type 1 endometrial cancer.
  Based on the large numbers and on the fact that risk reduction persists for many years, this is highly significant.

- Despite of the lower incidence of Type 2 endometrial cancer, also this association is significant and like with type 1 cancer, the effect persists for many years.
  Hence the protective effect on sarcoma remain questionable, since this association in the analysis 2015 is not significant.

Mechanisms of carcinoprotection in Type I EC using COC

(1) Progestogens block estrogen-dependent endometrial proliferation.

(2) Progestogen stimulates glandular epithelial secretory activity and deciduate transformation of stromal fibroblasts. These terminal differentiated cells can no longer proliferate and are shed in withdrawal bleedings (if implantation not occur).
  Simultaneously also potential (pre-)malignant cells can be eliminated!

(3) COC centrally and directly effects:
  Since endometrial activity of EE (from COC) is much lower compared to E2 and because of continuous progestin action, endometrial atrophy is achieved!

Mueck AO et al. Endocrine Related Cancer 2010; 17: 203-211
Mechanisms of carcinoprotection in Type 1 EC using COC

Much more changes in histological features during hormonal contraception (induced mainly through progestogen action) have been reported, like:

- different proliferatory, secretory and atrophic (like) patterns
- changes in gland-to-stroma ratio, in stromal factors (e.g. very potent G F s)
- effects on architectural structures (e.g. cribiform and/or papillary patterns)
- changes in glandular cellularity, cytoplasmic changes, mitotic activity
- changes in angiogenesis
- increase or decrease of cytologic atypia (powerful markers and predictors for progestogenic potency)

Mueck AO et al. Endocrine Related Cancer 2010; 17: 263-271

Mechanisms of carcinoprotection in Type 2 EC using COC

1. Increased decidual endometrial loss ("shedding") can lead to removal of premalignant or hyperplastic endometrial cells ("Shedding effects": same mechanisms like with IUD!)

2. Development and maintenance of endometrial atrophy through non-genomic progestogen-effects (P-g & PGRMC pathways)

3. Genomic progestogen effects primarily stimulated and mediated not by classical receptors (ER, PR), but e.g. via membrane-bound steroid receptors

Mueck AO et al. Endocrine Related Cancer 2010; 17: 263-271

OUTLOOK: Research on endometrial effects (endometrial safety) using sexual steroidal hormones (contraceptives and HRT)

Genomic and non-genomic progestogen action via different progestogen receptors

Bramley E, Reproduction 2003;125:3-15

Non-genomic pathways: Not well understood!

Leonhardt H et al. Steroids 2003;68:761-770

Progestogen-induced mechanisms of protein synthesis: Classical genomic pathway via nuclear receptors

Genentech et al. Gynecol 2002;100:717-73
PR-membrane-bound receptor is highly expressed in patients with breast cancer and also in some endometrial cancers, mediating strong-proliferating genomic and non-genomic effects of certain (but not all) progestogens via cross-talk with other cell components.

**Known function:** Involved in the development of certain cancers

**Potential function:** Involved in resistance mechanisms

---

**PGRMC1 Receptor: Structure and Expression in different tumors**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Human</th>
<th>Canine</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- membrane-associated progesterone receptor; MAPR protein family
- different from other steroid receptors in structure, function, localization
- Cytochrome b5 subunit + multiple functional interaction domains

**Known function:** Involved in the development of certain cancers

---

**PGRMC1 as mediator for genomic and non-genomic effects of some (but not all) progestogens**

- **ER-negative: non-genomic effects**
  - ER-negative genomic effects
  - Proliferation
  - Cyt P450
  - PI3K/Akt pathway
  - AKT: Proteinkinase B: key role in multiple cellular processes such as proliferation, transcription, cell migration, apoptosis, etc.

- **ER-positive: genomic effects**
  - ER-positive genomic effects
  - Proliferation
  - Cyt P450
  - PI3K/Akt pathway
  - AKT: Proteinkinase B: key role in multiple cellular processes such as proliferation, transcription, cell migration, apoptosis, etc.

**Function of PGRMC1 Receptor: Mediator for proliferation effects, demonstrated for certain progestogens in the breast**

- in vitro studies

**Function of PGRMC1 Receptor: Mediator for the development of resistance mechanisms against carciño-protective effects**

- first clinical studies in breast cancer patients

---

**Function of PGRMC1 Receptor: Mediator for proliferation effects, demonstrated for certain progestogens in the breast**

- animal studies

---

**Increased expression of progesterone receptor membrane component 1 is associated with aggressive phenotype and poor prognosis in ER-positive and -negative breast cancer**

**Ruan X, Mueck AO et al. Menopause 2017; 24: 203-209**
Progesterone regulates 100's of endometrial genes!

Columns = 43 endometrial samples

Rows = genes

Ongoing research on long-term progestogen effects on endometrium histology compared to physiological changes

Progestogens can inhibit Matrix Metallo-Proteinases (MMPs) which prevents degradation of extracellular matrix and which can avoid or stop uterine bleedings.

No bleeding!

Research on mechanisms of bleedings: Progestogens acting on MMPs of endometrium functionalis can avoid uterine bleedings

Physiological cyclical effect of progesterone

Therapeutic effect using COC, LNG-IUD or HRT

Regular withdrawal bleedings using sequential HRT

Progestogens can inhibit Matrix Metallo-Proteinases (MMPs) which prevents degradation of extracellular matrix and which can avoid or stop uterine bleedings.

No bleeding!
Progestogens acting on MMPs of endometrium basalis can induce inflammation which can lead to bleedings

Endometrial atrophy and basalis denudation

Strong exogenous progestogens

Endometrial atrophy and basalis denudation

Progestogens acting in the endometrium basalis layer, exogenous progestogens can induce inflammation leading to bleedings

Proteolytic MMPs are able to degrade extracellular matrix leading to uterine bleedings

Acting within the endometrium basalis layer, exogenous progestogens can induce extracellular matrix proteinases (MMPs) which can provoke local inflammation leading to bleedings which can be stopped with tetracyclines killing the MMPs.

Endometrial atrophy and basalis denudation

Take effect of strong, long acting progestins during use of COC or LNG-IUD: perhaps no negative effect on the risk for developing endometrial cancer

Progestogens acting on MMPs of endometrium basalis can induce inflammation which can lead to bleedings

Endometrial atrophy and basalis denudation

Strong exogenous progestogens

Endometrial atrophy and basalis denudation

Progestogens acting in the endometrium basalis layer, exogenous progestogens can induce inflammation leading to bleedings

Proteolytic MMPs are able to degrade extracellular matrix leading to uterine bleedings

Acting within the endometrium basalis layer, exogenous progestogens can induce inflammation leading to bleedings

Proteolytic MMPs are able to degrade extracellular matrix leading to uterine bleedings

Take effect of strong, long acting progestins during use of COC or LNG-IUD: perhaps no negative effect on the risk for developing endometrial cancer

Acknowledgement for great support of the Chinese Government in the field of Gynecological Endocrinology

Collaboration University of Tuebingen (Germany) and Capital Medical University, Beijing OB/GYN Hospital (China)

- daily > 5,500 outpatients
- total > 1.5 Million outpatients in 2017
- Dept. of Gynecological Endocrinology: about 160,000 outpatients in 2017

Beijing, China

First specialized OB/GYN Hospital in New China (1949)

- daily > 5,500 outpatients
- total > 1.5 Million outpatients in 2017
- Dept. of Gynecological Endocrinology: about 160,000 outpatients in 2017

- serving 40% of the patients in Beijing
- Beijing: > 25 Million inhabitants > 600 hospitals

Acknowledgement for great support of the Chinese Government in the field of Gynecological Endocrinology

Cooperation with University of Cologne, Germany (Prof. Roemer) for establishment of:

First Department of Outpatient Hysteroscopy in China

Research on endometrial effects using hormonal regimens, and now also used in routine practice of diagnosis and therapy

Endometrial cancer and contraception

ALFRED O. MUECK
MD. PharmD. PhD.
THANK YOU FOR YOUR ATTENTION!