TITLE: Copper Intra-uterine Devices as a Contraceptive for Adult Women: A Review of Clinical Effectiveness and Safety

DATE: 16 September 2013

CONTEXT AND POLICY ISSUES

There are numerous methods available to prevent pregnancy, making decisions surrounding the selection of contraceptive strategy potentially difficult. Factors to consider in this process include costs, duration of contraceptive effects, side effects, and others.

One method of contraception is the insertion of an intrauterine device (IUD). These devices exert their effects through a variety of mechanisms depending on their composition and whether hormones are released. There are currently 2 types of IUDs available within Canada: (1) levonorgestrel-releasing IUDs; (2) copper IUDs. Despite the use of IUDs as a commonly used method of reversible contraception internationally, use in Canada remain relatively low. In particular, experience with copper IUDs is even less owing to concerns regarding relative efficacy compared to other non-IUD and IUD options, as well as the risk of adverse events (e.g. uterine perforation, dysmenorrhea, pelvic inflammatory disease). The purpose of this review is to examine the evidence regarding the clinical efficacy and safety of copper IUDs.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of copper IUDs as a contraceptive for adult women?
2. What is the evidence for the safety of copper IUDs as a contraceptive for adult women?

KEY FINDINGS

Use of copper IUDs compared to other methods of contraception appears to be effective, but further research is needed to determine optimal use and safety.

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METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Results of a broader search (a more general subject heading) limited to health technology assessments, systematic reviews, meta-analyses were also included. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and August 14, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult women 18+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Copper intrauterine devices</td>
</tr>
<tr>
<td>Comparator</td>
<td>Non-copper IUDs</td>
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<tr>
<td></td>
<td>Oral contraceptives</td>
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<tr>
<td>Outcomes</td>
<td>Efficacy: pregnancy prevention</td>
</tr>
<tr>
<td></td>
<td>Safety: uterine perforation, dysmenorrhea (frequency and severity), pelvic inflammatory disease, other adverse effects</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs); non-randomized studies for safety only</td>
</tr>
</tbody>
</table>

IUD=intrauterine device;

Exclusion Criteria

Studies were excluded if they did not meet selection criteria, were duplicate publications or included in a systematic review or involved drugs and devices not available in Canada.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. RCT and non-randomized study quality were evaluated using the Downs and Black instrument. A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.
SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 310 citations. Upon screening titles and abstracts, 273 citations were excluded and 37 potentially relevant articles were retrieved for full-text review. One additional potentially relevant report was identified through grey literature searching. Of the 38 potentially relevant reports, 34 did not meet the inclusion criteria. Four publications were included in this review. Two systematic reviews and two cohort studies met inclusion criteria. No additional RCTs or evidence-based clinical practice guidelines were identified. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Details on study characteristics, critical appraisal and findings can be found in Appendices 2, 3 and 4, respectively.

Country of origin

Both systematic reviews, one from a group in the USA\(^7\) and one from the United Kingdom,\(^8\) included RCTs and observational studies from multiple different countries (including those in Asia, Europe – only USA in North America). Of the two remaining studies, one was carried out in Germany and Finland,\(^9\) and other in the USA.\(^10\)

Study setting

Both systematic reviews included RCTs conducted in the outpatient setting.\(^7,8\) The two observational studies were population based studies using local and national registry databases.\(^9,10\)

Patient population

All studies included adult women (≥18 years old) requiring contraception, with an overall age range of 18 to 50 years old. One observational study included women in the general population\(^9\) while the other\(^10\) studied women diagnosed with bipolar disorder. Both systematic reviews\(^7,8\) mostly included women in the general population with the exception of one systematic review,\(^8\) which included a study conducted in women with diabetes.

Interventions and comparators

All relevant studies identified in the French et al. systematic review compared copper IUDs of various models (>250mm\(^2\) or <250mm\(^2\)) versus levonorgestrel (LNG) IUDs. Copper IUDs categorized as >250mm\(^2\) included: CuT 380A (Cu: copper; T: T-shaped device) and CuT 380Ag IUDs and <250 mm\(^2\) included CuT 200 and CuT 220 IUDs.\(^8\) Steenland et al. included studies that used CuT 380A, CuT 380Ag, CuT 200 and CuT 220C IUDs.\(^7\) These were compared with various treatments including LNG IUDs, depot medroxyprogesterone acetate (DMPA), other non-hormonal IUDs and oral contraceptives (COCs), which were not specified.

Berenson et al. conducted a cohort study comparing CuT 380A with sterilization.\(^10\) Dinger et al. used compared LNG-IUD with all copper-IUD and the types of copper IUDs were not specified.\(^9\)
Outcomes measured

All studies reported on side effects or adverse events. The trials taken from the systematic review by French et al. included endpoints on pregnancy rates, discontinuation rates, menstrual changes, and any reported adverse reactions. Steenland et al. focused on adverse events with IUDs, specifically pelvic inflammatory disease (PID).

Dinger et al. reported the rates of breast cancer with LNG-IUD compared to copper IUDs with a case-control study design based on data obtained from local and national registries. Berenson et al. compared the rates of infectious and non-infectious complications. Infectious outcomes were gonoccal infections, inflammatory diseases of the female reproductive tract, and cervicitis/endocervitis. Non-infectious outcomes included pain associated with female genital organs, disorders of menstruation, accidental puncture or laceration, and mechanical complications of intrauterine devices.

Summary of Critical Appraisal

The quality of evidence identified varied. Of the two systematic reviews, French et al. demonstrated high methodological quality, providing an a priori design, comprehensive literature search (including grey literature), detailed summaries of all studies included (and clearly stated reasons for exclusion). The systematic review by Steenland et al. provided detailed summaries of all included with an assessment of quality/bias. However, the review of Steenland et al. was based upon a limited literature search (only one database, no grey literature search) and details of excluded studies were not stated. Neither systematic review assessed for the likelihood of publication bias.

Two observational studies were identified. Neither study was able to randomize or blind subjects, an inherent limitation of observational studies. The study by Berenson et al. reflected a subset of the American patients taken from a commercial health claims database, thereby limiting generalizability to individuals with bipolar disorder with a certain level of health coverage. Additionally, in the absence of randomization, no adjustments were made to reduce the impact of potential confounders (i.e. multiple regression analysis). No adjustments were stated for the multiple comparisons of categorical data, increasing the likelihood of detecting a statistically significant difference due to chance, rather than treatment effect. Conversely, this study may have been underpowered to detect any additional differences due to the small sample size. No power calculation was provided by either studies.

It is assumed that Dinger et al. reflects the general population in Finland and Germany, though the registries from which subjects were identified were not stated. Therefore this may limit generalizability to women in these countries. Adjustments were made to reduce the impact of reasonably selected potential confounders. Matching by birth year and area of residence was employed to reduce the impact of time-related bias and geographical differences between cases and controls.

Summary of Findings

Two systematic reviews and two observational studies compared the effects of copper IUDs with other forms of contraception, including LNG-IUD, DMPA, COCs and sterilization. In the systematic review by French et al., five trials compared LNG IUD vs. copper IUDs (>250
mm²). Data was not pooled for analysis. There was no significant difference in pregnancy due to method failure. No significant differences were demonstrated between LNG and CuT 380Ag IUDs in terms of prolonged bleeding at 3 months or 3 years. No data was collected for hormonal side effects. One study in their analysis showed LNG users were significantly less likely to experience painful menstruation. There were no differences in ectopic pregnancies or PID. The systematic review by Steenland et al. reviewed the rates of adverse effects across various forms of contraception, including copper IUD, LNG-IUD, COC and DMPA. No meta-analysis was conducted. Six studies reported rates of PID with IUDs and of these 4 studies included copper IUD as a comparator with LNG-IUD and DMPA. Each of these studies showed no differences between treatment groups. No studies with copper IUDs included in their review included events related to blood pressure or weight gain.

The two observational studies had similar findings. In Berenson et al., continuation rates were similar in CuT380A (86%) and LNG-IUS groups (87%). The rates between copper IUDs versus LNG-IUS were summarized in descriptive statistics (percentages, no standard deviations) for the following selected complications: inflammatory disease of the uterus/fallopian tubes (1.77% vs. 0.72%), cervicitis (1.8% vs. 1.1%) and dysmenorrhea (5.3% vs. 2.9%). Statistical analysis performed for ectopic pregnancies showed no statistically significant difference. In the study by Dinger et al., no statistically significant difference in breast cancer rates were seen between users of LNG-IUDs and copper IUDs, before and after adjustments for potential confounders (including age, area of residence, family history, age of menarche, medications).

Limitations

The largest limitation of the studies included in this report is generalizability. All studies, including those contained in both systematic reviews, were conducted internationally. Generalizability is further impaired by the small number of studies available for each comparison. In addition to the limitations discussed previously, these single studies may not be adequate to draw solid conclusions about efficacy and safety.

This review focused on adult women (aged 18 or older), and therefore excluded studies with any participants under 18 years of age. As such, the findings of this review may not be generalizable to a younger population. A list of these studies which did not meet inclusion criteria but may be of potential interest is available in Appendix 5.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This review found four studies relevant to the effectiveness and safety of copper IUDs. In general, the authors of these studies concluded no significant differences between copper IUDs and other methods of contraception with regards to pregnancy rates and adverse events.

Based on the limited evidence included in the review copper IUDs are likely as effective a method of contraception with low failure rates.

With regards to the safety, the use of copper IUDs was not shown to be associated with higher rates of breast cancer, in a large, well-designed case-control study. Though no signal for harm was seen in this review, each of these individual trials may have been underpowered to detect any difference in adverse event rates. Therefore, larger studies of adequate study design are required to draw definite conclusions regarding safety profiles.
Conclusions on the best practices regarding the use of copper IUD could not be drawn since relevant evidence-based guidelines were not identified.

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REFERENCES


APPENDIX 1: Selection of Included Studies

310 citations identified from electronic literature search and screened

273 citations excluded

37 potentially relevant articles retrieved for scrutiny (full text, if available)

1 potentially relevant report retrieved from other sources (grey literature, hand search)

38 potentially relevant reports

34 reports excluded:
- irrelevant population (4)
- irrelevant intervention (5)
- irrelevant comparator (12)
- irrelevant outcomes (5)
- other (review articles, editorials, no analysis) (8)

4 reports included in review
# APPENDIX 2: Summary of Study Characteristics

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Outcomes Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steenland, 2013, USA&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Systematic Review</td>
<td>15 studies (RCT and non-RCT studies) in women in ambulatory setting; 4 studied use of copper IUD</td>
<td>Levonorgestrel IUD</td>
<td>Copper IUD, COC, DMPA</td>
<td>PID, hypertension/blood pressure, migraine, weight gain</td>
</tr>
<tr>
<td>French, 2011, UK&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Systematic Review</td>
<td>25 RCTs with women of reproductive age (9 RCTs investigating copper IUD)</td>
<td>Levonorgestrel IUD</td>
<td>Copper IUDs (&gt; 250 mm&lt;sup&gt;2&lt;/sup&gt; or CuT 380A and CuT 380Ag) and &lt; 250 mm&lt;sup&gt;2&lt;/sup&gt; or CuT 200 and CuT 220</td>
<td>pregnancy, PID, and discontinuation side effects, menstrual side effects</td>
</tr>
<tr>
<td>Berenson, 2011, USA&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>849 women with diagnosis of bipolar disorder</td>
<td>CuT380A (n=114)</td>
<td>Sterilization (n=411) DMPA (n=184) LNG-IUD (n=140)</td>
<td>No efficacy outcomes; infectious and non-infectious, menstrual-related and mechanical complications</td>
</tr>
<tr>
<td>Dinger, 2011, Germany&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Case-control study</td>
<td>5113 cases of breast cancer 20, 452 controls &lt;50 years old</td>
<td>Copper IUD (unspecified)</td>
<td>LNG IUD</td>
<td>Risk of breast cancer</td>
</tr>
</tbody>
</table>

USA = United States of America; RCT = randomized control trial; IUD = intrauterine device; PID = pelvic inflammatory disease; UK = United Kingdom; CuT = T-shaped copper device; DMPA = depot medroxyprogesterone acetate; LNG = levonorgestrel;
# APPENDIX 3: Summary of Critical Appraisal

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
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<td></td>
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</tbody>
</table>
| Steenland, 2013, USA          | • Quality of studies appropriately assessed by two independent reviewers acknowledged in formulation of conclusions  
                               | • Potential conflict of interest acknowledged in included studies                          | • Limited search strategy; not clear if determined a priori  
                               |                                                                                           | • List of excluded studies not stated  
                               |                                                                                           | • Risk of publication bias not assessed                                                   |
| French, 2011, UK             | • Comprehensive literature search based on pre-defined criteria  
                               | • Summary of study characteristics and list of included and excluded studies provided       | • Quantitative analysis of <250 mm comparator included non-copper, non-hormonal IUDs  
                               |                                                                                           | • Risk of publication bias not assessed  
                               |                                                                                           | • Potential conflict of interest not acknowledged in both systematic review and included studies |
| **Observational Studies**    |                                                                           |                                                                                                |
| Berenson, 2011, USA          | • Objectives of study stated  
                               | • Interventions clearly stated described  
                               | • All adverse outcomes clearly documented                                                   | • Characteristics and source of data not well described  
                               |                                                                                           | • No randomization or blinding.  
                               |                                                                                           | • No adjustments to reduce potential confounding  
                               |                                                                                           | • No adjustment for multiple comparisons                                                   |
| Dinger, 2011, Germany        | • Objectives of study stated  
                               | • Large case-control series  
                               | • Reasonable matching and adjustments to reduce potential confounding and bias               | • No randomization or blinding.  
                               |                                                                                           | • Characteristics and source of data not well described                                   |

USA = United States of America; IUD = intrauterine device; UK = United Kingdom
### Systematic Reviews

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Author's Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steenland, 2013, USA&lt;sup&gt;7&lt;/sup&gt;</td>
<td>PID: Of 6 studies examining IUDs, 4 studies investigating copper IUD compared with other methods of contraception (LNG-IUD, DMPA). No data was pooled in the analysis. All studies showed NSS differences amongst the treatment groups. Hypertension &amp; Weight gain: no studies were identified studying copper IUDs.</td>
<td>“For studies examining PID after IUD insertion, there were no differences in incidence of PID, or IUD removal for PID, among women who had a copper IUD inserted compared with women who began using DMPA, a hormone-releasing IUD or COCs (Level I, good to II-2, fair)” P 623</td>
</tr>
<tr>
<td>French, 2011, UK&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Five trials compared LNG IUD vs. copper IUD (&gt;250 mm&lt;sup&gt;2&lt;/sup&gt;). Data was not pooled for analysis. There were no significant difference in pregnancy due to method failure. No significant differences were demonstrated between LNG and CuT 380Ag IUDs in terms of prolonged bleeding at 3 months or 3 years. No data was collected for hormonal side effects, though one study showed LNG users were significantly less likely to experience painful menstruation. No significant differences in ectopic pregnancies or PID. Only 1 trial (of 4 investigating IUD &lt;250 mm&lt;sup&gt;2&lt;/sup&gt;) used copper IUD as a comparator to LNG IUD. No differences in pregnancy due to method failure at 1, 2 or 3 years nor any difference in discontinuation rates for any reason.</td>
<td>“There was insufficient evidence to suggest a difference in the pregnancy rates between LNG-20 IUS users and IUD&gt;250mm2 users.” “We did find a lower risk of pregnancy when the LNG-20 IUS was compared to IUDs &lt;250mm2.” p.12</td>
</tr>
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</table>

### Observational Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Author's Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berenson, 2011, USA&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Continuation rates were similar in CuT380A (86%) and LNG-IUD groups (87%). Complications rates for copper IUD vs. LNG-IUD (descriptive only): Cervicitis: 1.8% vs. 1.1%</td>
<td>“More women with bipolar disorder continued using IUDs at one year than women using DMPA. The rates of complications and psychiatric hospitalizations were not different among women using an IUD, DMPA,</td>
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<tr>
<td>Dysmenorrhea: 5.3% vs. 2.9%</td>
<td>or sterilization.” Abstract. P. 1</td>
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<td>-----------------------------</td>
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<td>Ectopic pregnancies: NSS among all groups</td>
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</table>

**Dinger, 2011, Germany**

Matching and adjustment occurred for multiple variables (including age, area of residence, family history, age of menarche, medications)

No significant differences detected with or without adjustment between LNG-IUD and copper IUD

“In conclusion, our results do not give any indication that LNG-IUD is associated with an increased risk of breast cancer in women younger than 50 years of age.” P 216

USA = United States of America; RCT = randomized control trial; IUD = intrauterine device; PID = pelvic inflammatory disease; UK = United Kingdom; CuT = T-shaped copper device; DMPA = depot medroxyprogesterone acetate; LNG = levonorgestrel
Appendix 5: List of Potentially Relevant References

Including subjects aged <18 years old:


Comparison of different copper IUDs: