Copper T380 intrauterine device for emergency contraception: highly effective at any time in the menstrual cycle

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STUDY QUESTION: Does the efficacy of placing a copper intrauterine device (IUD) for emergency contraception (EC) to prevent pregnancy depend on menstrual cycle timing and timing of unprotected intercourse (UPI)?

SUMMARY ANSWER: If the urine pregnancy test is negative prior to IUD placement, the copper IUD is highly effective for EC at any point in the menstrual cycle.

WHAT IS KNOWN ALREADY: The use of the Copper T380A for EC has been encouraged by the failure of oral EC methods to decrease rates of unintended pregnancy and the documented success of the IUD in reducing unintended pregnancies. However scant data exist regarding the efficacy and safety of IUD insertion for EC when accounting for menstrual cycle timing and time since UPI.

STUDY DESIGN, SIZE, DURATION: This is a secondary analysis of data obtained from a previously published prospective cohort study of women who received the Copper T380A IUD for EC between July 1997 and January 2000. We included 1840 participants according to the study inclusion criteria of a known last menstrual period (LMP) and cycle lengths of 25–35 days.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The original study included women aged between 18 and 44 years who presented for EC at 18 sites throughout China and who had regular menstrual cycles between 24 and 42 days, a known LMP, UPI within 120 h (5 days) and a negative urine pregnancy test (cutoff < 25 IU/ml). Women with uncertain LMP dates were excluded. This study included only participants with cycle lengths of 25–35 days.

MAIN RESULTS AND THE ROLE OF CHANCE: Among the 1840 participants with usual cycle lengths of 25–35 days, 850 (46.2%) had their IUD inserted following UPI in the expected fertile window and 84 (4.6%) had the insertion > 5 days after the predicted ovulation day and 52 (2.8%) had the insertion > 5 days after UPI. There were no pregnancies in the first month among the 1771 women who had information available regarding their 1-month follow-up pregnancy test.

LIMITATIONS, REASONS FOR CAUTION: This was a secondary analysis of an observational study, and thus participants were not randomized to an alternative postcoital method. There were a small number of women who had UPI > 5 days after their predicted ovulation day thus limiting the confidence of assuring a low risk of pregnancy in this situation. The ovulation day was calculated based on the LMP prior to IUD insertion and not on the subsequent first day of menses following IUD insertion.

WIDER IMPLICATIONS OF THE FINDINGS: If the urine pregnancy test is negative prior to IUD placement, the copper IUD is likely to be effective for EC at almost any point in the menstrual cycle.

STUDY FUNDING/COMPETING INTEREST(S): The original study was funded by the UNDP/UNPFA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. The donors and sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit the paper for publication.

Key words: IUD / emergency contraception / menstrual cycle
Introduction

Emergency contraception (EC) includes a group of treatments available to women that can be used after unprotected intercourse (UPI) to reduce the risk of unplanned pregnancy. EC options available in the USA include several oral hormonal methods such as levonorgestrel, ulipristal acetate and use of a variety of combined hormonal contraceptive pills. Several studies report pregnancy rates of 1–3% with the use of these EC methods (Cheng et al., 2012). Pregnancy rates are even higher when these EC methods are used in women who have UPI in the fertile window (beginning 5 days before and ending 1 day after expected ovulation), who have an elevated BMI or who have repeat acts of UPI in the cycle when EC has already been used (Glavier et al., 2011). Previously, it was thought that wide availability of oral EC would decrease rates of unintended pregnancy and abortion, but this has not been the case. A recent systematic review of several well-conducted, large clinical trials showed no decrease in rates of unintended pregnancy or abortion even when EC was readily accessible (Raymond et al., 2007).

Renewed interest in use of the Copper T380A (CuT380A) IUD for EC has been encouraged by the failure of oral EC methods to decrease rates of unintended pregnancy. This is occurring at a time when UPI use within the general population is increasing and there is documented success linking increased IUD use with population reductions in unintended pregnancies. As an EC method, the copper IUD has superior efficacy to oral EC methods with a reported pregnancy rate of <0.1% (Cleland et al., 2012). It also has an efficacy that appears to be unaffected by BMI, timing of UPI or additional acts of UPI after placement. Superior efficacy of the CuT380A IUD to oral methods of EC is likely related to the differences in mechanism of action as the oral methods prevent ovulation while the IUD prevents fertilization and has a greater peri- and post-ovulatory effect (Gemzell-Danielsson et al., 2013). The CuT380A IUD further distinguishes itself from oral EC methods because it continues to provide highly effective contraception for up to 12 years after initial placement (Dean and Schwarz, 2011). Additionally, evidence suggests that women choosing the CuT380A IUD over oral levonorgestrel for EC have a lower rate of pregnancy at 1 year (Turok et al., 2012).

While the copper IUD has demonstrated excellent efficacy as a method of EC, there are scant data assessing how long after UPI the IUD can be safely inserted or whether cycle timing affects efficacy. With these current limitations in data, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) contraceptive guidelines advise that the copper IUD be used within 5 days of UPI. These recommendations are designed to avoid use after possible implantation, the common definition of the start of pregnancy, which usually occurs 8–10 days after ovulation but may occur as early as 6 days later (Wilcox et al., 1999). The guidelines also stipulate that when the time of ovulation can be estimated, the copper IUD may be inserted beyond 5 days after UPI if that day is not >5 days after ovulation. However, copper IUD insertion for EC has been reported to have occurred up to 10 days after UPI without pregnancy (Cleland et al., 2012). The objectives of this study are to describe the use of the CuT380A IUD for EC relative to menstrual cycle day for women who had UPI before, during or after the expected fertile window, as well as for women who had their IUD inserted >5 days after UPI or predicted ovulation.

Methods

These data were obtained from a previously published prospective observational trial of women who received the CuT380A IUD and were followed for 12 months (Wu et al., 2010). The original study was approved by the institutional review boards of the National Research Institute for Family Planning, Beijing, China, and the institutional review boards at each participating site as well as by the WHO Secretariat Committee on Research Involving Human Subjects. Briefly, the study design and methods included women between the ages of 18 and 44 years who presented for EC at 18 sites throughout China and who had regular menstrual cycles between 24 and 42 days, a known last menstrual period (LMP), UPI within 120 h (5 days) and a negative urine pregnancy test (cutoff <25 IU/ml). Women with uncertain LMP were excluded. Upon enrollment, data were gathered on the date of onset of the participant’s LMP, usual cycle length, expected date of onset of next menstruation and the date and time of UPI. The original study was designed to evaluate the efficacy of the CuT380A IUD as EC after one cycle in addition to the continued use of the CuT380A IUD up to 12 months after its placement as an EC method.

For this study, a secondary analysis was performed on data from women with menstrual cycle lengths of 25–35 days. Because menstrual cycle length can act as a gauge of ovulatory function and thus help determine risk of conception, we used this information to exclude women who had a low probability of conception. Data have shown fecundability to be highest in women with cycle lengths lasting 25–35 days (Small et al., 2006; Wise et al., 2011). Accordingly, this narrower range of cycle length was selected in order to exclude women with a low risk of pregnancy in that cycle, which could otherwise falsely elevate the efficacy of the IUD for EC. Participants reported their LMP and ‘usual length of spontaneous menstrual cycles’ by number of days. Figure 1 addresses the following calculations of markers within the menstrual cycle based on a sample participant with a usual cycle length of 28 days.

The published guidelines on IUD use as EC reference the relationship of UPI, ovulation, and the timing of IUD insertion. Corresponding to these guidelines, we analyzed the distribution of menstrual cycle day of UPI and IUD insertion. We provided one-sided 95% upper confidence limits for efficacy based on overall use, IUD insertion in the expected fertile window, use beyond 5 days after the predicted day of ovulation and use beyond 5 days after UPI. One-sided confidence intervals were based on the method proposed by Wilson (Brown et al., 2001). All data were analyzed using SAS System, version 9.2 (Cary, NC, USA).

Results

The original trial included 1963 women who received the CuT380A IUD for EC. This analysis excluded 123 women: 5 because no LMP date was recorded and 118 who had usual cycle lengths that did not meet the inclusion criteria. There were no pregnancies among the women excluded from this analysis. The present analysis includes 1840 participants, comprising 93.7% of the original participants. Participant demographics are presented in Table I along with the mean cycle day of IUD insertion for this group. The majority of participants had had a prior abortion and nulliparity was rare. The most common reason for seeking EC was no contraceptive use.

There were no pregnancies in the first month among the 1771 women who had information available regarding their 1-month follow-up pregnancy test. The point estimate for pregnancy for IUD EC users in this sample was 0% (95% CI = 0.0–0.15%). At 1 month after presentation for EC, 32 participants had discontinued the IUD and 37 were lost to follow-up. There were no pregnancies in the first 3 months including in those who had discontinued the IUD. Among the 84 women with
IUD insertion >5 days after the estimated day of ovulation, the one-sided 95% upper confidence limit for risk of pregnancy was 3.1%. Among the 52 women who had insertion >5 days after UPI, the one-sided 95% upper confidence limit for risk of pregnancy was 4.9%. Menstrual cycle timing for IUD insertion relative to time since UPI is provided in Table II. Over half of IUD insertions occurred between cycle days 9 and 15 as shown in Fig. 2. Figure 3 demonstrates the frequency with which participants had UPI in relation to their day of ovulation, denoted here as Day 0. Nearly half of women had UPI in the expected fertile window (highlighted in red on the graph), nearly half had UPI when they were at lowest risk in the pre-ovulatory period and the remainder had UPI in post-ovulatory period.

Discussion

Regardless of cycle timing, there were no pregnancies in this large group of CuT380A IUD EC users. Women seeking EC do not wish to be pregnant, yet are at risk of pregnancy due to using either no contraception or a less effective method. With recent data showing that IUDs and contraceptive implants are over 20 times more effective than combined hormonal methods at preventing pregnancy (Winner et al., 2012), the woman who presents for EC at the clinic presents an opportunity to discuss and promote the most effective methods of contraception, beginning with choice of method of EC.

A significant barrier to obtaining the CuT380A IUD as EC is whether or not the woman meets insertion guidelines. According to the World Health Organization’s Selected Practice Recommendations, the copper IUD can be inserted at any time, if it is reasonably certain that the woman is not pregnant. The copper IUD can also be inserted within 5 days of UPI as EC. When the day of ovulation can be estimated, the copper IUD also can be inserted beyond 5 days after intercourse, as long as insertion does not occur >5 days after ovulation (WHO, 2004). If the provider is not reasonably certain that the woman is not pregnant, the guidelines state that the woman should be provided with an alternative EC method and a bridge contraceptive method until the provider can be reasonably certain that she is not pregnant and can insert the IUD. This generally means waiting until the next menstrual period. Guidelines surrounding IUD insertion are more rigid than using other contraceptive methods, including oral EC methods, because evidence suggests that pregnancies among women with IUDs are at higher risk for complications such as spontaneous abortion, septic abortion, preterm delivery and chorioamnionitis (Brahmi et al., 2012).

While these data provide additional information on the low risk of pregnancy when a copper IUD is inserted after UPI and after a negative pregnancy test, there are several limitations in the analysis. For example, the data set does not include enough people who were at specific points in the cycle. Over half of IUD insertions occurred between cycle days 9 and 15 as shown in Fig. 2. Figure 3 demonstrates the frequency with which participants had UPI in relation to their day of ovulation, denoted here as Day 0. Nearly half of women had UPI in the expected fertile window (highlighted in red on the graph), nearly half had UPI when they were at lowest risk in the pre-ovulatory period and the remainder had UPI in post-ovulatory period.

Table I Demographics (n = 1840).

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>28.9 (4.5)</td>
</tr>
<tr>
<td>Menstrual cycle duration (days)</td>
<td>29.6 (1.8)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>89 (4.8)</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>1164 (63.3)</td>
</tr>
<tr>
<td>Prior use of EC</td>
<td>61 (3.3)</td>
</tr>
<tr>
<td>Reason seeking EC*</td>
<td></td>
</tr>
<tr>
<td>No method used</td>
<td>1438 (78.2)</td>
</tr>
<tr>
<td>Method failure</td>
<td>397 (21.6)</td>
</tr>
</tbody>
</table>

EC, emergency contraception; LMP, last menstrual period.
*Five women did not report a reason for seeking EC.
protect against any further intercourse in the month that a woman presents for EC. This is an advantage over oral methods of EC. The process of assessing the risk of pregnancy based on reported menstrual cycle day can be unreliable because of the variation in cycle day of ovulation and the uncertainty of LMP (Stirling and Glasier, 2002). WHO researchers have used the more accurate method of obtaining the first day of menses following EC use and then subtracting 14 days from this to predict ovulation. Utilizing this method they found that EC use peaked around the fertile window (Task Force, 1998). Due to limitations in gathering the 30-day follow-up data for this study, we chose to base the calculation of ovulation on the LMP day given at the time of enrollment and we found that the frequency of UPI peaked prior to the expected fertile window. This difference may represent a difference in the populations studied. However, when we compared the cycle day of IUD insertion based on the LMP day given at enrollment and the follow-up data, the results were similar (data not presented).

Women who had their UPI in the expected prefertile window are almost one half of included participants. While this group is at negligible risk of pregnancy from the act of UPI that prompted their EC visit, they may have benefited from having the IUD in place later in the cycle when further episodes of UPI would place them at greater risk of pregnancy. Following IUD insertion, this group had no pregnancies and almost certainly prevented some unintended pregnancies by having contraceptive protection not just for EC but also for the rest of the month.

If women have a negative urine pregnancy test, the Copper T380A IUD might be able to be inserted at almost any point in the menstrual cycle with a very low risk of pregnancy. However, there are obvious limitations on the confidence of this statement given the limited number of women who were beyond 5 days after UPI and beyond 5 days after the predicted day of ovulation.

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<table>
<thead>
<tr>
<th>Time since last intercourse</th>
<th>n (%)</th>
<th>Time to IUD insertion from LMP (in days)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>&lt; 12 h</td>
<td>312 (16.0)</td>
<td>12.8 (4.5)</td>
</tr>
<tr>
<td>12 to &lt; 24 h</td>
<td>406 (20.8)</td>
<td>12.1 (4.6)</td>
</tr>
<tr>
<td>24 to 48 h</td>
<td>645 (33.0)</td>
<td>12.7 (4.4)</td>
</tr>
<tr>
<td>48 to 72 h</td>
<td>301 (15.4)</td>
<td>13.0 (4.1)</td>
</tr>
<tr>
<td>72 to 96 h</td>
<td>183 (9.4)</td>
<td>13.6 (4.4)</td>
</tr>
<tr>
<td>&gt; 96 h</td>
<td>105 (5.4)</td>
<td>14.6 (4.3)</td>
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Table II Cycle timing of unprotected intercourse and IUD insertion.
of Planned Parenthood Research, Zhengzhou, Henan, China; (ix) Yuan Xinhua, Jiangsu Family Planning Institute, Nanjing, Jiangsu, China; (x) Song Si, Shanghai Institute of Planning Parenthood Research, Shanghai, China; (xi) Cheng Weiyu, Tianjin Municipal Research Institute for Family Planning, Tianjin, China; (xii) Zhang Wanping, Hebei Family Planning Research Institute, Shijiazhuang, Hebei, China; (xiii) Zhao Dongxiao, Shanxi Family Planning Research Institute, Taiyuan, Shanxi, China; (xiv) Zhong Chunli, Guizhou Research and Technical Guiding. Institute of Family Planning, Guiyang, Guizhou, China.

Authors’ roles
D.K.T. developed the design of the secondary analysis, directed the project and contributed significantly to the writing and revision of the manuscript. E.M.G. provided substantial contribution to the design of the project, interpretation of the data and critically revised and contributed to the written manuscript. The role of D.W. in the manuscript was the data management and statistical analysis of data. He also reviewed the statistical methods and results sections of the manuscript. A.D. assisted with manuscript drafting of background, methods and discussion, as well as with critical discussion of the paper. L.T. was involved in drafting and revising the final manuscript for submission. S.C.W. provided substantial contribution to the design of the project, directed the data collection and data management, and in addition, critically revised and contributed to the written manuscript. All authors read and approved the final manuscript.

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Conflict of interest
D.K.T. reports personal fees and non-financial support from Teva Women’s Health, grants and non-financial support from Bayer health care, grants from Medicines 360 and grants from Bioceptive, outside the submitted work. E.M.G. reports personal fees from Merck Pharmaceuticals and personal fees from Teva Women’s Health, for research outside the submitted work. A.D. reports research support from Teva Pharmaceuticals for projects not related to this work. There are no other disclosures.

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