Management of a perforated levonorgestrel-mediated intrauterine device—a pharmacokinetic study: Case report

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Intrauterine contraception is a widely used, highly effective method of birth control. Uterine perforation is a serious albeit rare complication with the use of an intrauterine device (IUD). Although uterine perforation by the levonorgestrel-releasing intrauterine system (LNG-IUS) has already been described, no plasma LNG concentrations in this setting were reported. Neither has the management of LNG-IUS been commented on to date. Two months after insertion of an LNG-IUS into a 33-year-old woman, it was noted to be in the peritoneal cavity. Laparoscopy for IUD removal was conducted 5 months after insertion. LNG and sex hormone-binding globulin plasma concentrations were measured prior to and following the laparoscopic removal of the IUD. Intra-peritoneal dislocated LNG-IUS resulted in plasma LNG levels 10 times higher (4.7 nmol/l) than the plasma level of LNG observed with LNG-IUS placed in utero. This high plasma LNG level suppresses ovulation. Therefore a misplaced LNG-IUS should be removed when pregnancy is desired.

Key words: intrauterine device/levonorgestrel/perforation/pharmacokinetics/progestagen

Introduction

Intrauterine contraception is a widely used and a highly effective means of birth control. Uterine perforation is a potential complication with the use of an intrauterine device (IUD). Although uterine perforation by the levonorgestrel-releasing intrauterine system (LNG-IUS) has already been reported (Andersson et al., 1998; Bobrow et al., 2000) the plasma LNG concentrations in this setting have not been determined.

Case report

A 33-year-old woman, gravida 2, para 2, with history of regular menstrual cycles and a Caesarean section for twin discordance at the 32nd week of her first pregnancy, opted for an LNG-IUD (Mirena®, Schering AG, Germany) for contraception. LNG-IUD was inserted 8 weeks following a normal vaginal delivery when she was experiencing her first menstrual bleeding postpartum. The patient was not breast-feeding at the time of the insertion. The procedure was reported to be uneventful.

Routine trans-vaginal sonogram performed 2 months following the procedure failed to demonstrate the device in utero. A radiograph of the pelvis confirmed the diagnosis of a misplaced intra-abdominal LNG-IUS. Laparoscopy for IUD removal was scheduled. The patient reported cessation of regular menses and intermittent spotting during the 5 months period until laparoscopy was conducted.

On laparoscopy, the uterus and the adnexae appeared normal. The perforation site was unidentified. An LNG-IUD was observed encased in mild peritoneal adhesions in the pouch of Douglas and was easily removed. The remainder of the procedure was uneventful and the patient was discharged normal. Plasma concentrations of LNG and sex hormone binding globulin (SHBG) were measured 1 day prior to the procedure and serially for 24 h following the laparoscopy. Assays for LNG determination were performed at the Steroid Research Laboratory in Helsinki, Finland, following the method described by Johansson et al. (2002)

Results

Intra-peritoneal dislocated LNG-IUS resulted in a plasma LNG concentration of 4.7 nmol/l. Twenty five hours following IUD removal, the plasma LNG level dropped by 15% (4.7 to 4 nmol/l) and the SHBG level rose by 13% (79.5 to 91 nmol/l) (SHBG normal range: 18–114 nmol/l) (Table I).
Discussion

To our knowledge, evaluation of LNG blood levels after perforation into the peritoneal cavity has never been undertaken. The peritoneum is known to have a great absorptive capacity, consequently, LNG blood levels are expected to be higher when the IUD is in the peritoneum than when in utero. Mirena® releases LNG into the uterine cavity, where it is quickly absorbed via the capillary network in the basal layer of the endometrium into the systemic circulation. Within a few weeks plasma LNG concentrations reach a plateau ranging from 0.4–0.6 nmol/l (Nilsson et al., 1986; Haukkamaa and Holma, 1996). LNG plasma concentrations achieved by Mirena® are lower than those seen with the subdermal LNG-containing implant (Norplant®), the combined oral contraception and the mini-pill (Nilsson et al., 1986; Diaz et al., 1987; Kuhnz et al., 1992; Pakarinen et al., 1999) (Table II). Usually this plasma level of LNG does not inhibit ovarian function (Xiao et al., 1990). The level of LNG after intra-peritoneal dislocation of Mirena® is similar to levels reported following combined oral contraceptive containing 0.15 mg LNG and 0.03 mg ethinyl estradiol (Microgynon®) administration (Kuhnz et al., 1992) (Table II). These higher LNG levels do not have an untoward effect, however they may suppress ovulation. The absence of cycle regularity and the vaginal bleeding pattern, reported by our patient, support this speculation. The amenorrhoea, reported in another case of a misplaced LNG-IUS, could be attributed to inhibition of ovulation (Bobrow et al., 2000).

The plasma concentration of LNG decreased moderately 25 h following its removal from the peritoneum. The half-life of elimination of plasma LNG after oral administration is estimated to be 20–25 h (Kuhnz et al., 1992; Nassr et al., 1997), however, following the removal of a LNG-containing subdermal implant, the decay rate of plasma LNG had a half life of 42 ± 16 h (range 13–62). It was shown that the major part of the steroid is cleared from the plasma within 96 h (Croxatto et al., 1988).

Plasma LNG is mainly bound to SHBG (64%) and to albumin (35%). The free fraction of LNG is only 1.3% (Kuhnz et al., 1992). SHBG is a plasma binding protein with high affinity to sex hormones such as testosterone, dihydrotestosterone, estradiol and LNG. A significant correlation was found between concentrations of LNG and SHBG, although a marked inter-individual variation of SHBG levels exists (Xiao et al., 1990; Jia et al., 1992; Kuhnz et al., 1992).

Plasma SHBG levels increased in our patient by 15%, 25 h following LNG-IUS removal. The concentrations of SHBG have been shown to decrease slightly during the use of oral LNG-containing contraceptive mini-pill, but not during the use of LNG-IUS (Pakarinen et al., 1999). LNG released from either subdermal or intrauterine devices is not subjected to a ‘first-pass’ effect of the liver, unlike LNG administered orally or released i.p. We presume that i.p. localization of LNG-IUS may result in increased hepatic exposure to LNG via the portal system, leading to decreased levels of SHBG.

Although no strong recommendations should be based on case reports, in the infrequent event of uterine perforation by an IUD, there is much to be learnt from each report. The very high level of plasma LNG originating from the i.p. misplaced LNG-IUS dictates a different therapeutic strategy towards its presence and its removal. I.p. LNG-medicated IUD may suppress ovulation, and could still be regarded as an effective contraception. When pregnancy is desired, the therapeutic approach differs from that of a copper IUD. The latter may be left intraperitoneally, especially if asymptomatic. In contrast, a misplaced LNG-IUS should be removed in order to permit ovulation.

Acknowledgement

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References


Table I. LNG and SHBG serum levels prior to and following LNG-IUD removal

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Date drawn</th>
<th>No of hours</th>
<th>LNG nmol/l</th>
<th>SHBG nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-laparoscopy</td>
<td>~2:00</td>
<td>4.7</td>
<td>79.5</td>
</tr>
<tr>
<td>2</td>
<td>Day of IUD removal-post laparoscopy</td>
<td>~2:00</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>~4:00</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>~6:00</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>~9:00</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>~11:00</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1st day post laparoscopy</td>
<td>~19:00</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>~25:00</td>
<td>4.0</td>
<td>91</td>
</tr>
</tbody>
</table>

Table II. Comparison of levonorgestrel (LNG) plasma concentrations for various methods of contraception

<table>
<thead>
<tr>
<th>Type of contraception</th>
<th>Plasma LNG levels (± SD) after steady state (nmol/l)</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microgynon® EE2 0.03 mg + LNG 0.15 mg</td>
<td>4–17 ± 3.7</td>
<td>9</td>
</tr>
<tr>
<td>Microluton® mini-pill LNG 30 μg</td>
<td>0.96 ± 0.65</td>
<td>13</td>
</tr>
<tr>
<td>Norplant®</td>
<td>0.93 ± 0.08</td>
<td>5</td>
</tr>
<tr>
<td>Mirena® in utero</td>
<td>0.44 ± 0.2</td>
<td>6,11–13</td>
</tr>
<tr>
<td>Mirena® in peritoneum</td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

EE2 = ethinyl estradiol
new formulation of the levonorgestrel intrauterine system and serum levonorgestrel concentration with the new formulation compared to that with the original one. Leiras Study Report, 1. No.02–89532–07.


Kuhnz, W., Al-Yacoub, G. and Fuhrmeister, A. (1992) Pharmacokinetics of levonorgestrel and ethinylestradiol in 9 women who received a low-dose oral contraceptive over a treatment period of 3 months and, after a wash-out phase, a single oral administration of the same contraceptive formulation. *Contraception*, 46, 455–469.


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