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Serum copper levels in users of multiload intra-uterine contraceptive devices

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Summary

The systemic absorption of copper incorporated into multiload intra-uterine contraceptive devices (IUDs), as indicated by serum copper levels in users of such devices, was assessed in a prospective longitudinal study. One hundred and ten healthy Nigerian women using either multiload copper 250 (MLCU 250) or multiload copper 375 (MLCU 375) IUDs participated in the study. Their serum copper levels were estimated serially during 12 months of continuous use of the devices. The mean ($\pm$ s.e.m.) pre-insertion serum copper levels of our subjects using MLCU 250 (17.0 $\pm$ 3 μmol/l) and MLCU 375 (16.7 $\pm$ 0.5 μmol/l) were found to be lower than those reported in Americans (22.2 μmol/l) and in Germans (20.2 μmol/l), although similar to levels in Indians (17.0 μmol/l). There was no significant difference in the mean serum copper levels estimated before and after 1 month of continuous use of the device. Serial estimations of the serum copper levels in users showed that there was no alteration in these levels after a period of 12 months of continuous IUD use.

We therefore conclude that the copper incorporated into multiload IUDs appears not to influence the concentration of serum copper of users.

Résumé

L'absorption systémique du cuivre incorporé dans des contraceptifs intrautérins multiload (IUD), comme indiqué, par les niveaux du cuivre dans le sérum qui sont présents dans les utilisatrices des tels contraceptifs, était évalué dans une étude longitudinale éventuelle. Cent-

dix femmes nigériannes qui sont en bonne santé et qui utilisent soit le multiload copper 250 (MLCU 250) soit le multiload copper 375 (MLCU 375) IUD ont participé à l'étude. Les niveaux de cuivre dans leur sérum furent estimés pendant les 12 mois d'usage continu de ces contraceptifs. Les niveaux moyens ($\pm$ s.e.m.) du cuivre dans le sérum de nos sujets, c'est-à-dire avant l'insertion, pour le MLCU 250 (17.0 $\pm$ 3 μmol/l) et le MLCU 375 (16.7 $\pm$ 0.5 μmol/l) étaient moins élevés que les chiffres rapportés de 22.2 μmol/l pour les Américaines et 20.0 μmol/l pour les Allemandes, mais similaires aux niveaux rapportés pour les Indiennes (17.0 μmol/l). Il n'y avait aucune différence significative dans les niveaux moyens du cuivre dans le sérum estimés avant et après 1 mois d'usage continue de ce contraceptif. En plus, les estimations en série des niveaux cuivreux du sérum dans les utilisateurs ont montré qu'il y'avait aucun changement dans ces niveaux pendant une periode de 12 mois d'usage continu de l'IUD.

Nous concluons donc, que le cuivre incorporé dans les IUD's multiload n'influt pas de façon apparent sur les niveaux cuivreux du sérum des utilisatrices.

Introduction

The intra-uterine contraceptive device (IUD) is used widely by Nigerians accepting modern methods of contraception. In a study by Otolorin *et al.* [1] in 1985, 71.3% of new family planning acceptors at University College Hospital, Ibadan chose IUDs. When the whole of the country is considered, 27% of overall acceptors of family planning methods are on IUDs [2]. The continued increase in people accepting IUDs in this population could stem from the

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strong aversion for operations and secrecy, and the long-term effectiveness associated with IUD use, and because such use is not coitus related.

The multiload copper IUDs were recently introduced into some family planning centres in Nigeria to replace the Lippes loop device. The production of this loop was discontinued because of financial losses incurred during litigations arising from complications associated with its use [3,4]. These multiload copper devices were designed to be better than the Lippes loop in terms of effectiveness and use-associated complications, and this has been confirmed by reports from developed countries [5,6].

Systemic absorption of copper from copper IUDs and subsequent exchange with endogenous copper has been observed in rats [7]. This caused concern regarding whether similar absorption occurs in humans using copper IUDs in which a rise in serum copper level could produce signs of toxicity. Hagenfeldt [8] has reported increased copper levels in intra-uterine secretions of copper T IUD users without a corresponding increase in their serum copper levels. Anteby et al. [9] have also demonstrated a systemic absorption of copper from a copper-containing latex IUD, but without a significant increase in the post-insertion serum copper level beyond the normal level in any of the users. In Nigeria, Olatunbosun et al. [10] reported no significant difference between serum copper levels in control subjects (i.e. with no contraception) and those using Lippes loops. However, in their study there was a significantly increased serum copper level in women using oral contraceptives compared to controls with no contraception, a change which they attributed to the increase in binding proteins which occurs in oral contraceptive users [10]. This study did not include women on copper IUDs. Our present study was therefore designed to evaluate prospectively over 12 months any effect of copper IUDs on serum copper levels in Nigerians using multiload copper devices.

Subjects and methods

Intra-uterine devices

The multiload IUD comprises a polyethylene stem and plastic side arms with serrated fins which ensure its adaptation to the uterine fundus without stretching the cavity. The MLCU 250 has 27 cm of copper wire (0.3 mm in diameter) wrapped around its polyethylene stem to provide a total surface area of 250 mm^2 of copper. The MLCU 375 contains copper with a surface area of 375 mm^2.

Subjects

One hundred and ten healthy menstruating Nigerian women presenting consecutively, who after counselling chose IUD as the only form of contraception for a period of at least 12 months of continuous usage, were recruited into the study. Their ages ranged between 20 and 40 years, and parity between 1–9 years. They all met the admission criteria stipulated in the producer's operating manual (Multiload copper intra-uterine devices manual: Organon Ltd, Cambridge U.K.). All gave informed consent for participation and had traceable home addresses in Ibadan, Nigeria. Each volunteer was allowed to pick at random a card labelled with a particular type of device. The corresponding device was then inserted into the woman's uterine cavity. Fifty-five women had MLCU 250 while the rest had MLCU 375. All insertions were performed at the Family Planning Clinic of the University College Hospital, Ibadan by two trained family planning nurses.

Protocol

Before insertion of each device 10 ml of blood was obtained from the antecubital vein of each subject and stored in a plain universal bottle. Subsequent samples were obtained at the end of the 1st, 4th, 8th and 12th month following insertion. After clot retraction the samples were centrifuged at 2500 g and the serum stored at −20°C until analysis. The serum copper estimation was carried out at the end of the 14th month following insertion of the device into the last subject.

Analysis

Each serum sample (0.5 ml) was initially acidified by addition of 0.2 ml 6 N hydrochloric acid followed by de-proteinization with 0.7 ml 40%

trichloro-acetic acid solution according to the method of Alfaro [11]. The concentration of copper in the supernatant was then measured with a Perkin Elmer atomic absorption spectrophotometer (model 403, Norwalk, U.S.A.) with a hollow copper cathode lamp as described by Sunderman and Roszel [12].

Statistics

All determinations were made in duplicate and data was stored and analysed by a microcomputer IBM Model AT using DATASTAR and SYSTAT software. Results are expressed as mean ± s.e.m. unless otherwise indicated.

The unpaired Student's *t*-test was used to determine the significance of difference between two means. The level of statistical significance was fixed at $P < 0.05$.

Results

Age and parity distribution

The age, parity and cycle day at insertion of either MLCU 250 or MLCU 375 are as indicated in Table 1. There were no significant differences in any of these parameters in either group.

Serum copper values

The serum copper levels pre-insertion and at follow-up are shown in Table 2 and Fig. 1. With MLCU 375 the pre-insertion serum copper level was 16.7 ± 0.5 µmol/l. At 4, 8 and 12 months following insertion serum copper values were 15.9 ± 0.4, 16.4 ± 0.5 and 16.1 ± 0.5 µmol/l respectively. In women using MLCU 250 the pre-insertion serum copper

Table 1. Age, parity and cycle day at insertion of IUD

Characteristics	MLCU 375	MLCU 250	P level
Age	30.8 ± 0.6*	31.9 ± 0.6	n.s.
Parity	4.4 ± 0.2	4.5 ± 0.2	n.s.
Cycle day at insertion	3.0 ± 0.2	2.8 ± 0.2	n.s.

*Values represent mean ± s.e.m.

Table 2. Mean serum copper level in users of each type of IUD before and after 1 month of use

Device	Mean serum copper level at insertion (µmol/l)	Mean serum copper level after 1 month of use (µmol/l)	t value
MLCU (*n*=55)			
Range	10.9–23.4	11.1–22.7	
Mean	16.7	16.4	0.7
s.e.m.	0.5	0.3	(P > 0.05)
MLCU 250 (*n*=55)			
Range	11.3–23.9	11.3–24.2	
Mean	17.0	16.7	0.7
s.e.m.	0.3	0.3	(P > 0.05)

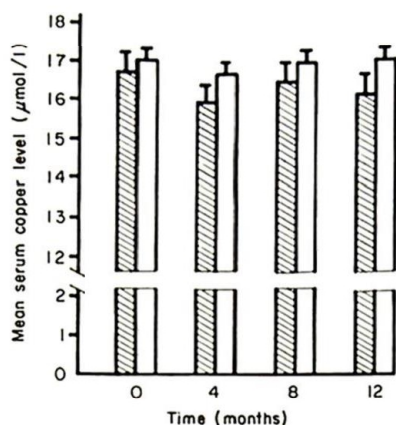**Fig. 1.** Composite bar chart showing changes in mean serum copper levels at 4-monthly intervals post-insertion of either MLCU 250 (□) or MLCU 375 (□). Values represent means ± s.e.m.

level was 17.0 ± 0.3 μmol/l while at 4, 8 and 12 months it was 16.6 ± 0.3, 16.9 ± 0.3 and 17.0 ± 0.3 μmol/l. At no time and for no specific IUD did serum copper levels differ pre- or post-insertion.

Discussion

The mean pre-insertion serum copper levels of the subjects using either MLCU 375 or MLCU 250 are similar to the values of 17.2 μmol/l reported by Olatunbosun *et al.* [10] in a similar group of Nigerian women using the Lippes loop. These levels are lower than those observed in Americans and Israelis (22.2 μmol/l) [13,14], and in Germans (20.2 μmol/l) [17], but similar to those reported for Indians (17.0 μmol/l) [15]. This difference in the serum copper levels between the women from developed countries (Americans and Germans) and those from developing countries (Nigeria and India) has been attributed to possible biological differences in the synthesis of transport proteins in plasma; this may have resulted in a reduction in the albumin : globulin ratio in women from developing countries [10].

The use of multiload copper IUDs did not appear to affect the serum copper in this study. This is similar to the finding of Prema *et al.* [15] in India using copper T 200 IUDs, but at variance with the report of Anteby *et al.* [9]

using latex leaf IUDs which contain zinc and copper. In their study, Anteby *et al.* [9] reported an increase in serum copper levels post-insertion in women in whom the pre-insertion level was lower than normal. This increased level was within the normal range for their population.

Hagenfeldt [8] assessed the quantity of copper in uterine secretions of copper IUD users and reported that the rate of release of copper from copper IUDs *in utero* was greater during the 1st month post-insertion than the release rate during subsequent months. If that observation were applicable generally, one might expect maximal absorption of copper from intra-uterine secretions and a resultant increase in serum copper level in women using copper-containing devices in the first month of use. However, this was not observed here as the serum copper levels pre-insertion and at 1 month post-insertion were very similar (Table 2). Our results support a variety of studies on experimental animals and Caucasians in whom there is no evidence of accumulation of copper in tissues and body fluids of users of copper IUDs [8,9,16,17]. This might therefore indicate, although not necessarily conclusively prove, either that copper is not absorbed to any significant extent from intra-uterine multiload copper devices or that it is immediately cleared from the body once it is absorbed. Whatever happens in the body, it is possible to predict with a measure of confidence that systemic copper is unlikely to accumulate with prolonged use of copper containing IUDs.

Acknowledgment

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