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Contraception 87 (2013) 486–496

Contraception

Review article

Hemoglobin and serum ferritin levels in women using copper-releasing or levonorgestrel-releasing intrauterine devices: a systematic review

Richard F. Lowe[a], Ndola Prata[b,*]

[a]Venture Strategies Innovations, Berkeley, CA 94704, USA

[b]Bixby Center for Population, Health and Sustainability, Berkeley, CA 94720, USA

Received 23 August 2011; revised 3 September 2012; accepted 21 September 2012

Abstract

Background: The use of intrauterine devices as a contraceptive method has been steadily growing in developing countries. Anemia in reproductive-age women is a growing concern in those settings.

Study Design: A systematic review of studies with measured hemoglobin and serum ferritin at baseline and after 1 year of use of copper intrauterine devices (IUDs) or a levonorgestrel-releasing intrauterine system (LNG IUS) was performed.

Results: Fourteen studies involving copper IUDs in nonanemic women and 4 studies in anemic women and 6 involving the LNG IUS met the criteria for the systematic review. Meta-analyses for hemoglobin changes showed significant decreases for users of copper IUDs and an increase for the LNG IUS, but with limited data. In general, ferritin levels followed the same pattern.

Conclusion: Decreases in hemoglobin mean values in copper IUD users were not sufficient to induce anemia in previously nonanemic women. Women who are borderline anemic would likely benefit from using the LNG IUS.

Keywords: Hemoglobin; Serum ferritin; Copper IUD; Levonorgestrel IUD; Anemia

1. Introduction

The World Health Organization estimates that 42% of women in nonindustrialized countries and around 20% of women in industrialized countries are anemic [1]. A blood hemoglobin level of 120 g/L and a serum ferritin level of 15 ng/mL are considered the cutoffs below which a nonpregnant woman is determined to be anemic [2]. Despite the fact that the normal level of serum ferritin, 250 ng/mL, does not itself represent an appreciable amount of iron, the serum ferritin level is considered to be a faithful reflection of body iron stores and, together with hemoglobin, is used to assess a person's iron status. The daily iron requirement for an adult woman of reproductive age is around 2.0 mg.

In developing countries, menstruation has been posited to be a risk factor for anemia. This risk can be exacerbated when women suffer from other vaginal bleeding disorders, have poor nutritional status and are affected by parasite infections [3–5].

Monthly blood loss at menstruation can be affected by the use of intrauterine devices (IUDs). The main side effect of using a copper IUD is increased or prolonged vaginal bleeding [6]. The late 1980s saw the development of the levonorgestrel-releasing intrauterine system (LNG IUS) called Mirena®, which releases daily 20 mcg of the hormone directly into the uterus for between 5 and 7 years [7–9]. As well as having excellent contraceptive efficacy [10,11], the device also has a number of therapeutic effects. The reduction of menstrual blood loss has been the subject of numerous reviews [12–15].

The LNG IUS has been determined to be an effective treatment for menorrhagia [16] and a good alternative to hysterectomy in premenopausal women [17]. The reduction in the volume of monthly blood loss (MBL) resulting from insertion of the LNG IUS should result in an increase in iron levels in the body and reduce the prevalence of anemia among this group of women. A systematic review of controlled trials and case series showed that MBL decreased by between 75% and 98% [18]. For severely anemic women,

* Corresponding author. Scientific Director, Bixby Center for Population Health and Sustainability, School of Public Health, University of California, Berkeley, 229 University Hall, Berkeley, CA 94720-6390. Tel.: +1 510 643 4284.

E-mail address: ndola@berkeley.edu (N. Prata).

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http://dx.doi.org/10.1016/j.contraception.2012.09.025

it would appear that this treatment alone would probably not be sufficient to prevent anemia, a conclusion also reached by Sivin [15].

The belief that normal menstruation is a risk factor for iron-deficient anemia has recently been challenged in a study that concluded that endometrial thickness is dependent on energy levels, which themselves are correlated to iron levels [19]. A thicker endometrium should thus result in a woman having higher iron levels, and normal menstruation should not affect iron levels and should not be a risk factor for anemia. However, this study was conducted with normal, nonanemic women, and so the findings cannot be extrapolated to a population of anemic women.

If hemoglobin and ferritin levels are increased in menorrhagic women using the LNG IUS, then it is reasonable to assume that there could also be increases in women who menstruate normally. Simultaneously, do levels of these chemicals decrease in women using copper IUDs, which are known to increase MBL, in the course of the first year of use? Copper IUDs are used extensively in countries in the Middle East and Asia, regions that are also known to have high proportions of women who are anemic or iron deficient and potentially have poor health. If copper IUDs decrease iron stores to levels associated with anemia, these women might benefit from use of an LNG IUS, which might increase levels of hemoglobin and ferritin.

This review attempts to answer two fundamental issues to consider when using a copper IUD or the LNG IUS:

1. In normally menstruating women, does use of a copper IUD decrease hemoglobin and ferritin levels? If so, would decreases be sufficient to induce anemia in previously nonanemic woman?
2. In normally menstruating nonanemic women, does use of the LNG IUS increase hemoglobin and ferritin levels?

2. Methods

2.1. Literature search

MEDLINE (via PubMed), Embase, NHS Centre for Reviews and Dissemination (DARE), The Cochrane Library and Popline® were searched for relevant studies. Reference lists in journal articles were also searched. No time limits or language restrictions were enforced. Medical subject headings (MeSH) used included *intrauterine devices copper, intrauterine devices medicated, levonorgestrel, progesterone*, *progestins*, *menorrhagia* and *anemia.* The term *"iron OR ferritin OR hemoglobin OR hemoglobin OR hematocrit OR haematocrit"* was also used as a search term in combinations with the MeSH search terms.

2.2. Selection

Criteria for initial review of the reference articles were that hemoglobin or ferritin levels were measured (blood or serum) in participating women at some point during the study. Studies were excluded if they did not contain information on levels of hemoglobin or ferritin in the blood or serum. In the second review, the following inclusion criteria for women were applied:

- normally menstruating at the start of the study (no studies involving menorrhagic women) and between the ages of 18 and 46 years
- mean normal hemoglobin levels at the start of the study ($\geq$120 g/L) or, if the study was specifically conducted in anemic women, not have a mean level $\leq$90 g/L
- mean values of hemoglobin and/or ferritin measured at baseline and at 12 months or a value for the mean difference between these two time periods
- use of the following copper IUDs: TCu 200, TCu 220C, TCu 380Ag (also known as TCu 380A), Nova-T 380, Multiload 250 (ML250) and Multiload 375 (ML375), and Fincoid
- The LNG IUS limited to the Mirena® LNG IUS releasing 20 mcg/day of LNG

Studies including multiple types of IUDs were included, and the review was conducted under the assumption that the presence of any amount of copper and not the surface area of copper on the IUD influences the changes in MBL and consequently the levels of hemoglobin or ferritin. Included in this review are randomized and nonrandomized studies with either open or single-blinded subjects. However, meta-analysis was conducted using the randomized studies.

The primary outcome measure was hemoglobin, and the secondary outcome was serum ferritin levels.

2.3. Data extraction

The review was carried out in accordance with the recommendations of the QUOROM statement [20]. A checklist was used to extract data and included information for study design, inclusion criteria, size, duration, loss to follow-up, termination of treatment and outcome results. When possible, study authors were contacted for clarifications and request for more complete information. Two reviewers carried out data extraction and compiled data. All studies were assessed for methodological quality in the following areas: method of randomization (if applicable), reporting of exclusion criteria of patient groups, number and detail determination of loss to follow-up, blinding (if applicable), and description and reporting of statistical methods used in the analysis.

2.4. Data analysis

Stata version 10 (manufactured in College Station, TX, USA, by StataCorp LP) was used for the statistical analysis [21]. Fixed effects and random effects models were used to calculate and compare pooled results. However, we present only results from the random effects models that better account for heterogeneity observed during the analysis. Due to continuous primary outcomes, standardized mean