Melatonin supplementation during controlled ovarian stimulation for women undergoing assisted reproductive technology: systematic review and meta-analysis of randomized controlled trials

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Objective: To examine the best evidence available regarding the effect of melatonin supplementation during controlled ovarian stimulation (COS) on the main assisted reproductive technology (ART) outcomes.
Design: Systematic review and meta-analysis of randomized clinical trials (RCT).
Setting: Not applicable.
Patient(s): Women undergoing COS for ART.
Intervention(s): Melatonin supplementation during COS for women undergoing ART.
Main Outcome Measure(s): Live birth rate, clinical pregnancy rate, number of retrieved oocytes, miscarriage rate, ovarian hyperstimulation syndrome (OHSS) rate, and number of congenital abnormalities. Comparisons were performed using risk ratio (RR) or mean difference (MD).
Result(s): Five RCTs were considered eligible, and their data were extracted and included in a meta-analysis. No studies reported live-birth or congenital abnormalities. Our estimates were imprecise for distinguishing between no effect and benefit considering clinical pregnancy (RR, 1.21; 95% confidence interval [CI], 0.98–1.50, five studies, 680 women, low quality-evidence) and the number of oocytes retrieved (MD, 0.6; 95% CI, −0.2–2.2, five studies, 680 women, low quality-evidence). Our estimates were imprecise for distinguishing among harm, no effect, and benefit considering miscarriage (RR, 1.07; 95% CI, 0.43–2.68, two studies, 143 clinical pregnancies, low quality-evidence) and interventions to reduce the risk of OHSS (RR,1.01; 95% CI, 0.33–3.08, one study, 358 women, low quality-evidence).
Conclusion(s): More studies investigating the role of melatonin supplementation are still needed before recommending its use in clinical practice. (Fertil Steril® 2014;101:154–61. ©2014 by American Society for Reproductive Medicine.)
Key Words: Melatonin, assisted reproductive techniques, ovulation induction, review

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Subfertility is defined as not being able to conceive after 1 year, which means being less fertile than a typical couple (1). Subfertility is a very common condition, affecting approximately 15% of reproductive age women (2, 3), and assisted reproductive technology (ART) is widely used to treat this condition. ARTs include interventions that require the

in vitro handling of both human oocytes and sperm or of embryos with the objective of achieving pregnancy and live birth (4). Currently, the chance of achieving a live birth after an ART cycle is close to 30% (5), and several strategies aiming to improve this rate are currently being tested (6–8).

Oxidative stress is indicated as a possible cause of poor oocyte quality, which can affect female reproduction (9). Several antioxidant enzymes (e.g., catalase, glutathione peroxidase, superoxide dismutase) protect oocytes and embryos from oxidative stress (9, 10). Melatonin also protects cells from oxidative stress by acting as a free radical scavenger and by stimulating antioxidant enzymes (11). Therefore, melatonin supplementation during controlled ovarian stimulation (COS) could protect oocytes from oxidative stress, which has a theoretical potential of improving the reproductive outcomes of women undergoing ART. The effect of this intervention on reproductive outcomes was already investigated by some randomized controlled trials (RCTs), and a systematic review and meta-analysis on this subject would be interesting to evaluate the quality of the current evidence, which would permit more robust conclusions.

Our objective is to evaluate the effectiveness and safety of melatonin supplementation during COS in women undergoing ART by performing a systematic review and meta-analysis of the existing RCTs.

MATERIALS AND METHODS

Protocol and Registration

The protocol of this review was registered at PROSPERO (CRD42013004258).

Eligibility Criteria

Only RCTs were considered eligible; quasi or pseudorandomized trials were not included. Cross-over trials were included only if data regarding the first treatment of each participant were available. Women undergoing COS for ART were the study participants and the intervention was melatonin supplementation versus placebo or no treatment during COS.

Information Sources

We searched for RCTs in the following electronic databases, on April 3, 2013, from their inception: Cochrane Central Register of Controlled Trials (CENTRAL); Cumulative Index to Nursing and Allied Health Literature (CINAHL) (www.ebscohost.com/cinahl/); Embase; Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS); Medical Literature Analysis and Retrieval System Online (MEDLINE); and PsycINFO. We searched for study protocols and ongoing trials in the following trials registers: ClinicalTrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com/isrctn/); and World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx). We searched for grey literature in Open Grey (www.opengrey.eu/).

Search

The following terms were used, adjusting for each database as necessary: ((melatonin) OR (pineal)) AND ((in vitro fertilization*) OR (in vitro fertilisation*) OR (IVF) OR (test-tube) OR (Intracytoplasmic Sperm Injection*) OR (ICSI) OR (reproduct*) OR (embryo transfer) OR (blastocyst transfer)) AND ((trial) OR (random*)). Additionally, we hand-searched the reference list from included trials and similar reviews.

Study Selection

Titles and abstracts were reviewed independently by two authors (L.M.D.S. and V.M.S.L.), checking for duplicates and using the pre-established criteria for inclusion. The same authors further evaluated the eligibility of potentially eligible records; disagreements were solved by consulting another author (W.P.M). Authors corresponds with the original study investigators to clarify study eligibility if required. There was no limitation regarding language, publication date, or publication status.

Data Collection Process

We extracted data from included trials using a data extraction form designed and pilot tested by the authors. In case we identified a study with multiple publications, we used the main trial report as reference and additional details were supplemented from secondary papers. We corresponded with study investigators to solve any query, as required. Data were extracted independently in a standardized manner by two authors (L.M.D.S. and V.M.S.L.) and checked by another (R.M.M.); disagreements were solved by consulting another author (W.P.M.).

Data Items

The study characteristics were authors, country, institution, funding sources, conflicts of interest, informed consent, ethical approval, study design, period of enrollment, inclusion criteria, exclusion criteria, number of participants in each group at each stage, age, and body mass index (BMI; mean $\pm$ SD) of participants in each group, and proportion of IVF/intracytoplasmic sperm injection (ICSI) in each group.

The primary outcome was live birth per allocated woman (birth of twins/triplets counted as a single live birth). The secondary outcomes were clinical pregnancy per allocated woman, ovarian hyperstimulation syndrome (OHSS; any form or the use of any intervention to reduce its risk) per allocated woman, number of oocytes retrieved per allocated woman, miscarriage per clinical pregnancy, and congenital abnormality per clinical pregnancy. Single fetal demise in twin or triplet pregnancies did not count as miscarriage.

Dealing with Missing Data

We contacted the study authors to obtain missing data. Where they were unobtainable, we assumed that clinical pregnancy (and subsequent miscarriage or live birth) did not occur and that no oocyte was retrieved from women with cycle