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

cancellation. No assumption was made for women who were lost to follow-up for another reason.

Implantation rate (number of gestational sacs observed divided by the number of embryos transferred) was not included in the quantitative meta-analysis because the denominator was not actually randomized. However, the implantation rates in each study were reported for completeness in Table 1.

Risk of Bias in Individual Studies

Two authors (R.M.M. and W.P.M.) independently assessed the risk of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias (e.g., difference in the number of embryos transferred, age of participants, cointerventions, early stopping). Disagreements were solved by consensus among these authors. To judge the risk of bias, we followed the Cochrane Collaboration's criteria for judging risk of bias (12): the trials were classified as being of low, high, or unclear risk of bias.

Summary Measures

The effects of the intervention were summarized as risk ratio (RR) for binary outcomes (live birth, clinical pregnancy, miscarriage, congenital abnormality) and as mean difference (MD) for continuous outcomes (number of oocytes retrieved). The precision of the estimates were evaluated by the 95% CI. We considered the clinical relevance of all comparisons taking into account the precision of the estimates; we had planned to determine the number needed to treat for an additional beneficial outcome or an additional harmful outcome when a significant difference was observed in the binary outcomes.

Synthesis of Results

All results were combined for meta-analysis using Review Manager 5.1 (Nordic Cochrane Centre, Cochrane Collaboration, 2011). Heterogeneity was assessed by the I^2 statistic. An increase in the risk of a particular outcome associated with melatonin that may be beneficial (e.g., live birth) or detrimental (e.g., miscarriage) was displayed graphically in the forest plots to the right of the center line and a decrease in the risk of an outcome to the left of the center line (Figs. 1 and 2 and Supplemental Figs. 3 and 4).

Risk of Bias across Studies

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the authors aimed to minimize their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If 10 or more studies were included, we planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Additional Analyses

When substantial heterogeneity was observed ($I^2>50\%$) we would address it by [1] rechecking data, [2] excluding studies with a high risk of bias (sensitivity analysis), and [3] performing subgroup analysis. If substantial heterogeneity persisted, we would subjectively choose between using a random-effects meta-analysis or not perform the meta-analysis for that outcome.

We had planned to perform subgroup analyses for live birth and clinical pregnancy if substantial heterogeneity was observed. We would separate studies by the characteristics of included participants: [1]unselected women or women with predicted normal ovarian response; [2] only women with polycystic ovary syndrome (PCOS) or with predicted high response (high risk of OHSS); [3] only women with predicted poor ovarian response or endometriosis.

Overall Quality of the Body of Evidence: Summary of Findings (SoF) Table

A summary of findings table was generated using GRADEPRO software. The quality of the evidence for the main review outcomes was evaluated using the following GRADE criteria: we considered the limitations of included (i.e., high risk of bias), inconsistency of effect, imprecision, indirectness, and publication bias. Judgments about evidence quality (high, moderate, low, or very low) are justified, documented, and incorporated into reporting of results for each outcome (13).

RESULTS

Study Selection

The electronic search was run on April –3, 2013, and a total of 429 records were retrieved: CENTRAL = 8; CINAHL = 1; Embase = 348; LILACS = 1; MEDLINE = 67; PsycINFO = 3; ClinicalTrials = 1; no additional record was obtained from Controlled-trials, WHO International Trials Registry Platform, OpenGrey, or by hand-searching the reference list of included studies and related reviews. We excluded 423 records after reading titles and abstracts: 64 were duplicates and 359 clearly did not meet the eligibility criteria. We further examined six records for eligibility: five studies were included in our quantitative analysis (14–18), and one study was excluded because it was not randomized (19). The study flow diagram is shown in Supplemental Figure 1.

Study Characteristics

Five studies were included in the quantitative analysis, and their characteristics are reported in Table 1. In one study, both participants and care providers were blinded (18), and the other four studies were not blinded. All five studies had parallel design and were single centered: three were conducted in Italy (16–18) and two in Turkey (14, 15). We tried to contact authors from all studies, but additional details were provided for only two studies (17, 18). One study was published as a conference abstract (17); one study is completed but still not published (18); and the other three studies were published as full articles (14–16).

TABLE 1

Characteristics of included studies.

Study	Country	Funding sources	Conflict of interests	Ethical approval	Signed informed consent	Study design	Period of inclusion	Inclusion criteria	Exclusion criteria	Interventions	Age	BMI, kg/m^2	Implantation rate, %	IVF/ ICSI
Batioglu 2012	Turkey	NR	None declared	NR	NR	Parallel design	NR	Primary infertility; age 20–40 years; regular menstrual cycles (21–35 days); no hormonal or non-hormonal therapy for at least the last 3 months; no systemic illness	Endometriosis, serious male factor (azoospermia), hypogonadotropic hypogonadism, FSH >13	Melatonin 3 mg/day vs. no treatment	30.4 ± 5.6 vs. 29.7 ± 4.9; *P*=.50	NR	NR	Only IVF
Eryilmaz 2011	Turkey	NR	None declared	Yes	Yes	Parallel design	January 2010 to December 2010	Diagnosis of disturbed sleep status by the psychologist. No ovulatory problem, normal hysterosal -pingography or laparoscopy, and a normal semen sample	Chronic drug usage, history of total fertilization failure cycles, hypertension, diabetes mellitus, uterine myoma and/or ovarian cyst, and smoking	Melatonin 3 mg/day orally from day 3–5 of menstrual cycle until the day of hCG vs. no treatment	30.1 ± 4.0 vs. 29.9 ± 3.6; *P*=NS	25.7 ± 4.5 vs. 26.1 ± 3.5; *P*=NS	28.5 vs. 27.0; *P*=NS	Only IVF
Nazzaro 2011	Italy	NR	NR	Yes	Yes	Parallel design	NR	Polycystic ovary syndrome (PCOS) by the ESHRE/ ASRM consensus, first IVF cycle, age between 26 and 38 years	Previous pelvic surgery; endometriosis; hydrosalpinx; uterine myomas; thrombophilic state	Myoinositol + folic acid + melatonin vs. myoinositol + folic acid	NR	NR	NR	Only IVF
Pacchiarotti 2013	Italy	NR	2 of 7 authors were working at Lo.Li. Pharma Int.	NR	Yes	Parallel design	July 2009 to December 2011	Age between 27 and 38 years with serum levels of FSH on day 3 of the ovarian cycle <12 IU/L; Rotterdam criteria for PCOS and BMI of 20–26 kg/m^2	Tubal, uterine, genetics and male causes of infertility and previous IVF treatment	Myoinositol (4 g/day) + folic acid (400 mg/day) + melatonin (3 mg/day) vs. myoinositol (4 g/day) + folic acid (400 mg/day)	31.2 ± 2.1 vs. 31.5 ± 2.8; *P*=NS	22.8 ± 1.3 vs. 23.1 ± 1.7; *P*=NS	13.8 vs. 12.2; *P*=NS	Only ICSI
Rizzo 2010	Italy	NR	NR	Yes	Yes	Parallel design	NR	Age between 35 and 42 years, with low oocyte quality detected in the previous IVF cycles	NR	Myoinositol (4 g/day) + folic acid (400 mg/day) + melatonin (3 mg/day) vs. myoinositol (4 g/day) + folic acid (400 mg/day)	37.8 ± 2.6 vs. 38.1 ± 2.0; *P*=NS	26.7 ± 2.78 vs 27.5 ± 2.2; *P*=NS	19.3 vs. 16.2; *P*=NS	Only IVF

Note: NS = nonsignificant; NR = not reported.

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Participants. A total of 680 women undergoing ART from five studies were included: 336 were allocated to use melatonin supplementation during COS, and 344 were allocated not to use melatonin. The eligibility criteria, and therefore the characteristics of the included participants, were completely different across studies (Table 1): women with primary infertility, aged between 20 and 40 years, with regular menstrual cycles (14); women with disturbed sleep status diagnosed by a psychologist, no ovulatory problem, normal hysterosalpingography or laparoscopy, and a normal semen sample (15); women with PCOS by the European Society Human Reproduction and Ambryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus, first IVF cycle, aged between 26 and 38 years (17); women with PCOS by the ESHRE/ASRM consensus, aged between 27 and 38 years, day 3 FSH <12 IU/L, and BMI of 20–26 kg/m^2 (19); women aged between 35 and 42 years, with low oocyte quality detected in the previous IVF cycles (16).

Interventions. Two studies compared melatonin supplementation (3 mg/day) during COS vs. no treatment (14, 15), and the other three studies compared supplementation with melatonin + standard treatment (folic acid + myoinositol) versus standard treatment (folic acid + myoinositol) (16–18): two studies used the following doses: myoinositol, 4 g/day, folic acid, 400 mg/day, and melatonin, 3 mg/day (16, 18); the other study did not report the doses used (17).

Outcomes. No study reported live birth or congenital abnormality; five of five reported clinical pregnancy; two of five reported miscarriage; five of five reported the number of oocytes retrieved; and one of five reported interventions to reduce the risk of OHSS (no case of OHSS was observed).

Risk of Bias within Studies

The risk of bias summary of the included studies is reported in Supplemental Figure 2. Three studies applied adequate methods (14, 17, 18), and two studies did not report which method was used (15, 16). Only two studies reported having concealed the allocation using sealed envelopes (17, 18). Only one study blinded the participants and care providers (18). The embryologists from three studies were blinded to the allocation (15, 17, 18), and the other two studies did not report whether the outcome assessor was blinded (15, 16).

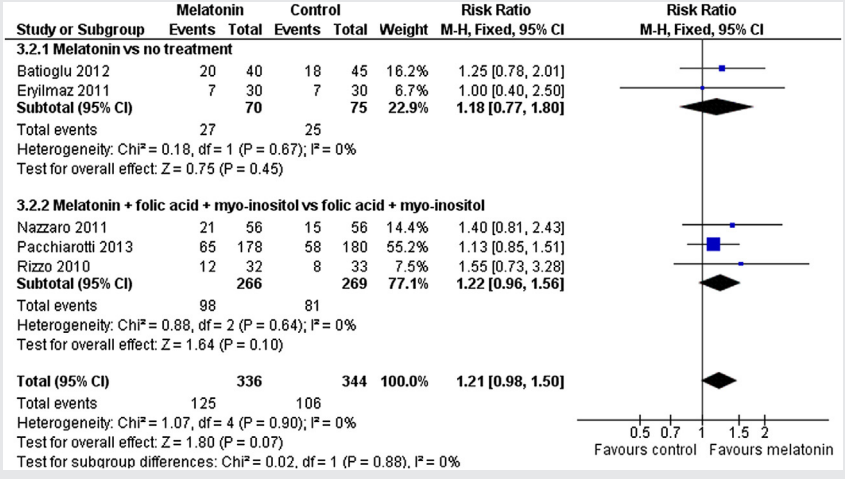
Four of five studies were judged to be at an unclear risk of bias: Authors from two studies stated that any cycle would be cancelled if the E_2 level was >4,000 pg/mL because of the high risk for OHSS, but they did not report whether any cycle was cancelled (14, 16). In one study three participants were excluded from analysis after randomization owing to either incorrect ingestion of the melatonin or cancellation of the IVF cycle (15). Another study did not state clearly whether data from all participants were included in the analysis (16). Still another study was judged to be at low risk of attrition bias (18) because the investigators reported what happened to all participants and we could analyze all data respecting the intent-to-treat principle—all patients who dropped out of the study after randomization had their cycles cancelled, and so it was safe to assume that no clinical pregnancy occurred and that no oocyte was retrieved.

One study was judged to be at unclear risk of bias for citing OHSS and miscarriage as secondary objectives but not reporting these outcomes in the results (17). We did not suspect any other source of bias for any of the included studies. The results for the individual studies are reported in the forest plots (Figs. 1 and 2 and Supplemental Figs. 3 and 4).

Synthesis of Results

1. No study reported this outcome.
2. Clinical pregnancy per allocated woman: melatonin versusno treatment/standard treatment. Our estimate was

FIGURE 1



Forest plot for clinical pregnancy per allocated woman.

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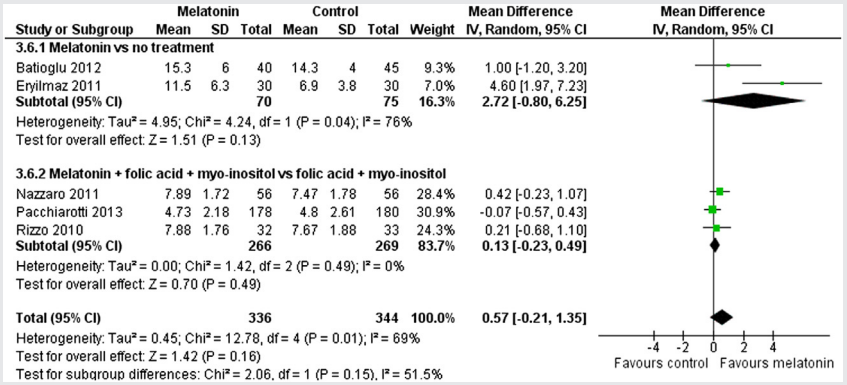
FIGURE 2



Forest plot for the number of oocytes retrieved per allocated woman.

Seko. Melatonin for assisted reproduction. Fertil Steril 2014.

not sufficiently precise to identify whether melatonin supplementation during COS caused no effect or benefit in clinical pregnancy: RR, 1.21; 95% CI, 0.98–1.50; $P=.07$, five studies, 680 women, $I^2 = 0\%$, low-quality evidence (Fig. 1).

Sensitivity analysis: Including only the study considered to be at low risk of bias (18) provided similar results: RR, 1.13; 95% CI, 0.85–1.51; $P=.39$, one study, 358 women.

3. Total number of oocytes retrieved. A large heterogeneity across studies was observed, and our estimate was not sufficiently precise to identify whether melatonin supplementation during COS caused no effect or benefit in this outcome: MD, 0.6 oocytes; 95% CI, −0.2–1.4; $P=.16$, five studies, 680 women, $I^2 = 69\%$, low-quality evidence (Fig. 2).

   Sensitivity analysis: Including only the study considered to be at low risk of bias, our estimate was compatible with no relevant effect of melatonin on the number of oocytes retrieved: MD, −0.07; 95% CI, −0.57–0.43; $P=.78$, one study, 358 women.

4. OHSS per allocated woman. Only one study reported the need of interventions to reduce the risk of OHSS (Supplemental Fig. 3): there were six cases of cycle cancellation because of excessive ovarian response in each group (RR, 1.01; 95% CI, 0.33–3.08; $P=.98$, one study, 358 women, low-quality evidence). No case of real OHSS occurred in any of the groups. This study was considered to be at low risk of bias.

5. Miscarriage per clinical pregnancy. Our estimate was not sufficiently precise to identify whether melatonin supplementation during COS caused harm, no effect, or a benefit: RR, 1.07; 95% CI, 0.43–2.68; $P=.89$, two studies, 143 pregnant women, $I^2 = 0\%$, low-quality evidence. Both studies reporting this outcome compared melatonin + standard treatment with standard treatment (Supplemental Fig. 4).

   Sensitivity analysis: Considering only the study judged to be at low risk of bias provided similar results: RR, 1.25; 95% CI, 0.43–3.72; $P=.69$, 123 pregnant women.

Risk of Bias across Studies

We did not identify any evidence of publication bias. However, the analysis is suboptimal since we did not perform funnel plot analysis because fewer than 10 studies were included.

Additional Analyses

We did not determine the number needed to treat because no significant difference was observed for the binary outcomes. However, we decided to subgroup the studies by the different comparisons observed in the included studies (melatonin vs. no treatment, and melatonin + folic acid + myoinositol vs. folic acid + myoinositol) for clinical pregnancy and number of oocytes retrieved (Figs. 1 and 2). Considering clinical pregnancy, the pooled results were very similar between these two subgroups: both estimates were not sufficiently precise to identify whether melatonin supplementation during COS caused no effect or benefit. Regarding the number of oocytes retrieved: [1] In the subgroup "melatonin versus no treatment," a substantial heterogeneity ($I^2 = 76\%$) was observed, and no meaningful conclusion can be drawn; [2] in the subgroup "melatonin + folic acid + myoinositol versus folic acid + myo-inositol," no heterogeneity across studies was observed, and the estimate was sufficiently precise to identify that adding melatonin to folic acid + myoinositol does not relevantly change the number of oocytes retrieved: MD, 0.1 oocytes; 95% CI, −0.2–0.5; $P=.49$, three studies, 535 women, $I^2 = 0\%$.

Sensitivity analyses, restricting the inclusion criteria to studies judged not to be at high risk of bias, were reported along with the main results.

DISCUSSION

Summary of the Evidence

Five studies were included for the comparison melatonin supplementation versus no melatonin supplementation, three of them comparing melatonin plus myoinositol and folic acid versus myoinositol and folic acid and two of them comparing melatonin versus no treatment (Table 2). No study reported

TABLE 2

Summary of findings: comparison between with and without melatonin supplementation.

	Absolute risks[a] (95% CI)				
	Assumed risk, controls	Corresponding risk,[a] melatonin	Relative risks (95% CI)	Participants (no. of studies)	Quality of the evidence
Clinical pregnancy per allocated women, %	31	37 (30–47)	1.21 (0.98–1.50)	680 (5)	Low[b]
Interventions to reduce the risk of OHSS, %	3	3	1.01 (0.33–3.08)	358 (1)	Low[c]
Total no. of retrieved oocytes	6.9	The mean no. of oocytes retrieved was 0.6 higher (from 0.2 lower to 1.4 higher)	3 (1-9)	680 (5)	Low[d]
Miscarriage per clinical pregnancy, %	11	11 (5–29)	1.07 (0.43–2.68)	143 (2)	Low[c]

Note: GRADE Working Group grades of evidence: high quality = further research is very unlikely to change our confidence in the estimate of effect; moderate quality = further research is likely to have an important impact in our confidence in the estimate of effect and may change the estimate; low quality = further research is very likely to have an important impact in our confidence in the estimate of effect and is likely to change the estimate; very low quality = we are very uncertain about the estimate.

[a] The assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded one level because of imprecision and one level because of the quality of the included studies.

[c] Downgraded two levels because of serious imprecision.

[d] Downgraded one level because of inconsistency and one level because of the quality of the included studies.

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live birth or congenital abnormalities. All five studies reported clinical pregnancy rates, but the pooled effect estimate was not precise enough to define no effect or benefit for this outcome; subgroup analyses separating the studies that compared melatonin with no treatment and the studies that compared melatonin + standard treatment with standard treatment alone provided similar results. For the number of oocytes retrieved, a large heterogeneity was observed considering all included studies and no meaningful conclusion could be drawn; however, the results considering only the study judged to be at low risk of bias and in the subgroup "melatonin + folic acid + myoinositol versus folic acid + myoinositol," permitted the conclusion that adding melatonin to folic acid + myoinositol does not relevantly change the number of oocytes retrieved. We are still uncertain of the effect on miscarriage rates and OHSS, since the estimates for these two outcomes were not precise enough to define whether melatonin supplementation during COS is associated with harm, no effect, or benefit.

Limitations

The included studies were imprecise, and only one study was judged to be at low risk of bias, reducing the quality of the evidence. In addition, none of the studies reported live-birth rates as an outcome, which is the most important patient-centered outcome of the intervention effect. The small number of included RCTs made the assessment of publication bias and reporting bias suboptimal, because of the impossibility of performing a funnel plot analysis.

Quality of the Evidence. In the comparison "melatonin versus no melatonin," the evidence was considered to be of low quality for clinical pregnancy, being downgraded one level because of imprecision (wide 95% CI) and another level because of the quality of the included studies. The evidence was considered to be of low quality for the need of interventions to reduce the risk of OHSS and was downgraded two levels because of serious imprecision. The evidence for the number of retrieved oocytes was considered to be of low quality and was downgraded one level because of inconsistency and one additional level because of the quality of the included studies. For miscarriage rates, the evidence was considered to be of low quality and was downgraded two levels for serious imprecision.

Overall Completeness and Applicability of the Evidence. Beyond the five studies included in the quantitative analysis, one additional study (Tamura et al. 2008) (19) addressed the review question but was excluded from the meta-analysis for not being a randomized study. It reported clinical pregnancy rates in women with previously failed IVF-ET cycles using melatonin supplementation vs. no melatonin (RR, 1.93; 95% CI, 0.77–4.87; P=.16, 115 women) but also did not report on live-birth rates. A systematic review addressing the effects of the use of any oral supplementation with antioxidants in subfertile females undergoing ART has recently been published (20). This systematic review pooled the results for any of the following: combinations of antioxidants, pentoxifylline, N-acetyl-cysteine, melatonin, L-arginine, vitamin E, myoinositol, vitamin C, vitamin D + calcium, and omega-3-polyunsaturated fatty acids. The results from this review do not permit us to draw conclusions about the specific efficacy of melatonin supplementation, as no separate analysis was performed. However, the observed results for clinical pregnancy considering all antioxidants were similar to the present review: the observed estimate was not sufficiently precise to identify whether the use of antioxidants causes no benefit (odds ratio = 1.30; 95% CI, 0.92–1.85). Although there is biological plausibility in using melatonin supplementation for improving oocyte quality and pregnancy rates in women undergoing ART, particularly in those who have already failed previous cycles of IVF/ICSI, we are still uncertain of its effects on patient-important outcomes, like live-birth rates and miscarriage rates. Future research is justified to address the question posed by the review, preferably reporting live-birth rates.

Conclusions

We are still uncertain of the effects of melatonin supplementation on the most important reproductive outcomes, namely,

live birth, miscarriage, OHSS, and congenital abnormalities. Melatonin supplementation during COS does not reduce the chance of clinical pregnancy and the number of oocytes retrieved, but we are uncertain whether there is benefit or no effect. Adding melatonin to myoinositol + folic acid is unlikely to cause a relevant change in the number of oocytes retrieved. Larger studies investigating the role of melatonin in improving ART outcomes are still needed before recommending its use in clinical practice.

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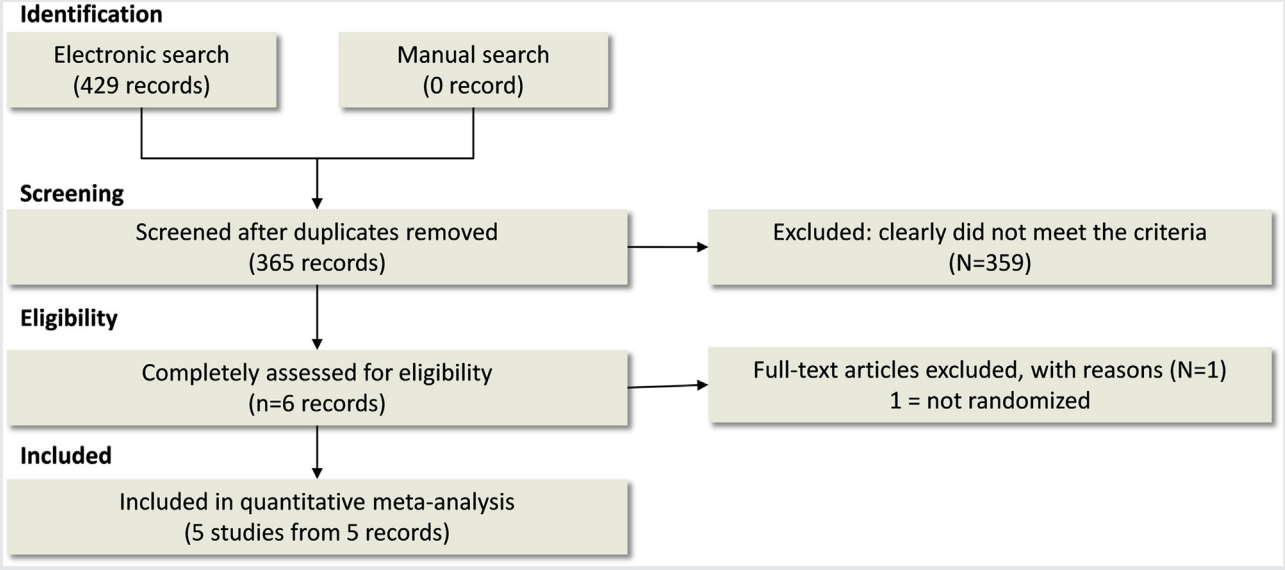
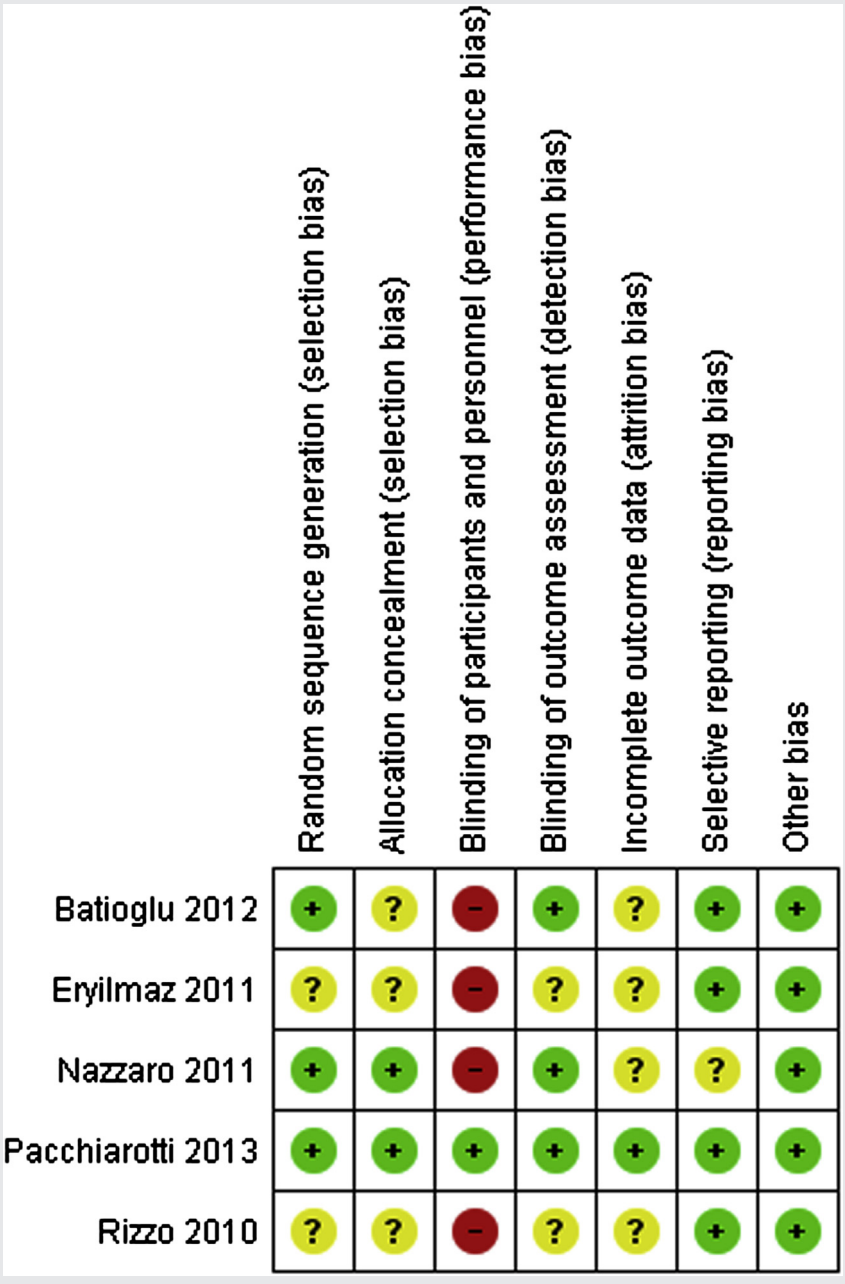
SUPPLEMENTAL FIGURE 1



Flowchart of study selection.

Seko. Melatonin for assisted reproduction. Fertil Steril 2014.

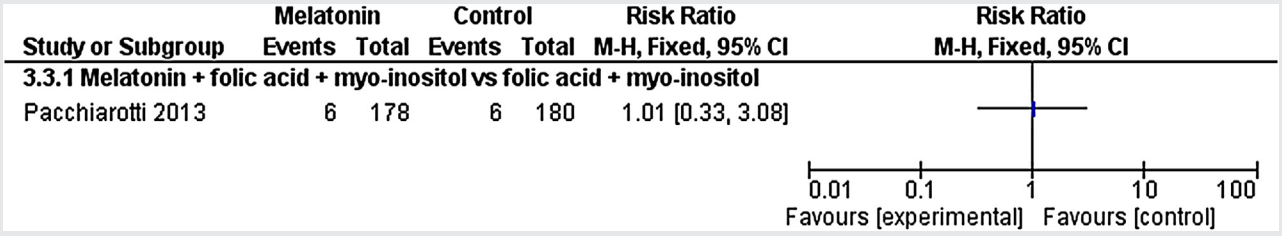
SUPPLEMENTAL FIGURE 2



Risk of bias summary for the included studies.

Seko. Melatonin for assisted reproduction. Fertil Steril 2014.

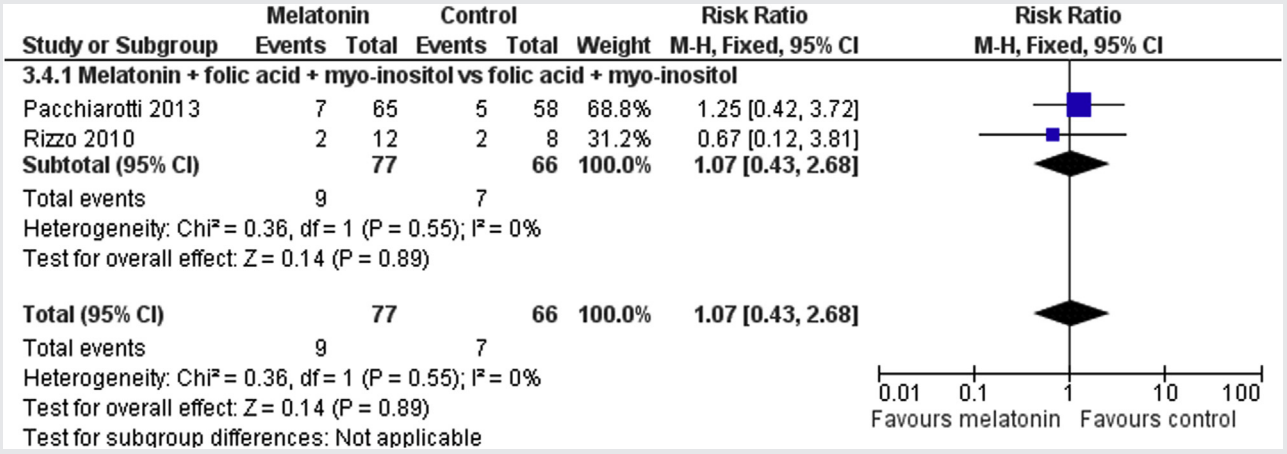
SUPPLEMENTAL FIGURE 3



Forest plot for the use of interventions to reduce the risk of developing OHSS per allocated woman.

Seko. Melatonin for assisted reproduction. Fertil Steril 2014.

SUPPLEMENTAL FIGURE 4



Forest plot for miscarriage per clinical pregnancy.

Seko. Melatonin for assisted reproduction. Fertil Steril 2014.